PB84-219187

Environmental Cancer and Heart and Lung Disease Annual Report to Congress (6th)

Technical Resources, Inc., Bethesda, MD

Prepared for

Task Force on Environmental Cancer and
Heart and Lung Disease, Washington, DC

Aug 83

U.S. Department of Commerce
National Technical Information Service
NTIS

PB84-219187

ENVIRONMENTAL CANCER
AND
HEART AND LUNG DISEASE

SIXTH ANNUAL REPORT TO CONGRESS

August 1983

TASK FORCE ON
ENVIRONMENTAL CANCER AND HEART AND LUNG DISEASE

U.S. Environmental Protection Agency • National Cancer Institute
National Heart, Lung, and Blood Institute • National Institute for Occupational Safety and Health
National Institute of Environmental Health Sciences • National Center for Health Statistics
Centers for Disease Control • Food and Drug Administration
Department of Energy

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

50272-101

REPORT DOCUMENTATION PAGE

1. REPORT NO.

2.

3. Recipient's Accession No. PB84 219187

4. Title and Subtitle
Environmental Cancer and Heart and Lung Disease
Sixth Annual Report to Congress

5. Report Date August 1983

6.

7. Author(s)
Task Force on Environmental Cancer and Heart and Lung Disease

8. Performing Organization Rept. No.

9. Performing Organization Name and Address
Technical Resources, Inc.
10215 Fernwood Road, Suite 408
Bethesda, Maryland 20817

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C) 68-02-3775
(G)

12. Sponsoring Organization Name and Address
U.S. Environmental Protection Agency
Task Force on Environmental Cancer and Heart and Lung Disease
401 M Street, SW., Office of Research and Development (RD672)
Washington, D.C. 20460

13. Type of Report & Period Covered
Annual Report to Congress
9/82 to 8/83

14.

15. Supplementary Notes
Task Force Chairman, William Ruckelshaus, Administrator
Task Force Working Group Chairman, Maria Pavlova, M.D., Ph.D.
Technical and Logistical Support, Technical Resources, Inc. under EPA Contract 68-02-3775

16. Abstract (Limit: 200 words)

The Sixth Annual Report to Congress describes the activities of the Task Force on Environmental Cancer and Heart and Lung Disease between September, 1982, and August, 1983. The Task Force Working Group and its project groups continued to coordinate interagency activities regarding the relationship between environmental pollution and human disease and the development of research recommendations aimed at reducing or preventing the incidence of environmentally related disease. The Task Force sponsored two important workshops targeting (1) the relationship between environmental factors and nononcogenic lung disease, and (2) the assessment of human exposure to environmental pollutants. A resulting Task Force recommendation to Congress calls for longitudinal studies of human populations as a basis for quantifying risk factors in the causation and aggravation of a group of lung diseases and for designing cost-effective prevention strategies. Other recommendations encourage support of legislative proposals to facilitate access to data required in the conduct of epidemiological studies and the continuation and improvement of the National Death Index under the NCHS. In addition to detailed discussions of the workshops, this report includes descriptions of ongoing Task Force activities, a list of Task Force publications, and a comprehensive bibliography on environmentally related nononcogenic lung disease.

17. Document Analysis a. Descriptors

Cancer, heart, lung, diseases, blood diseases, environmental cancer, environmental diseases, heart diseases, lung diseases, metabolic diseases, occupational diseases, respiratory diseases, epidemiology, etiology, public health, safety, pollution, toxicology, preventive medicine.

b. Identifiers/Open-Ended Terms

Environmental health, occupational health, research planning, research strategy, Federal Agency, committees, interagency

c. COSATI Field/Group

18. Availability Statement: Release unlimited

19. Security Class (This Report) Unclassified

20. Security Class (This Page) Unclassified

21. No. of Pages 112

22. Price

(See ANSI-Z39.18)

See Instructions on Reverse

OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

ENVIRONMENTAL CANCER
AND
HEART AND LUNG DISEASE
SIXTH ANNUAL REPORT TO CONGRESS

August 1983

TASK FORCE ON

ENVIRONMENTAL CANCER AND HEART AND LUNG DISEASE

U.S. Environmental Protection Agency
National Cancer Institute
National Heart, Lung, and Blood Institute
National Institute for Occupational Safety and Health
National Institute of Environmental Health Sciences
National Center for Health Statistics
Centers for Disease Control
Food and Drug Administration
Department of Energy

Prepared by the Task Force Working Group
Maria Pavlova, Chairperson

Copies of this document may be obtained free-of-charge through requests to

Technical Resources, Inc.
10215 Fernwood Road, Suite 408
Bethesda, Maryland 20817
(301-493-5300)

When this supply is exhausted, the document can be purchased from

National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road
Springfield, Virginia 22161

TASK FORCE ON
ENVIRONMENTAL CANCER AND HEART AND LUNG DISEASE

Please address your reply to:

William D. Ruckelshaus
Administrator
U.S. Environmental Protection
Agency
Washington, D.C. 20460

FEB 17 1984

Honorable George Bush
President of the Senate
Washington, D.C. 20510

Dear Mr. President:

As Chairman of the Task Force on Environmental Cancer and Heart and Lung Disease, I am pleased to submit the Sixth Annual Report to Congress in accordance with Public Law 95-95, Section 402(b)(5).

The Task Force continues to be an effective mechanism for enhancing interagency cooperation in the study of environment/disease relationships. During this past year, the Task Force sponsored workshops on exposure assessment and nononcogenic lung disease, which are summarized in this report. The findings and recommendations from these workshops will be published in the scientific literature and will constitute important contributions to the state of scientific knowledge.

The active participation of all the member Agencies serves to promote interagency information exchange and research coordination in the area of environmental health. These interactions can only have a positive impact on the continuing effort to improve our understanding of the possible relationships between environmental factors and human disease.

Sincerely,

William D. Ruckelshaus
Chairman

Environmental Protection Agency • National Cancer Institute
National Heart, Lung and Blood Institute • National Institute for Occupational Safety and Health
National Institute of Environmental Health Sciences • National Center for Health Statistics
Centers for Disease Control • Food and Drug Administration

TASK FORCE ON
ENVIRONMENTAL CANCER AND HEART AND LUNG DISEASE

Please address your reply to:
William D. Ruckelshaus
Administrator
U.S. Environmental Protection
Agency
Washington, D.C. 20460

FEB 17 1984

Honorable Thomas P. O'Neill, Jr.
Speaker of the House of Representatives
Washington, D.C. 20515

Dear Mr. Speaker:

As Chairman of the Task Force on Environmental Cancer and Heart and Lung Disease, I am pleased to submit the Sixth Annual Report to Congress in accordance with Public Law 95-95, Section 402(b)(5).

The Task Force continues to be an effective mechanism for enhancing interagency cooperation in the study of environment/disease relationships. During this past year, the Task Force sponsored workshops on exposure assessment and nononcogenic lung disease, which are summarized in this report. The findings and recommendations from these workshops will be published in the scientific literature and will constitute important contributions to the state of scientific knowledge.

The active participation of all the member Agencies serves to promote interagency information exchange and research coordination in the area of environmental health. These interactions can only have a positive impact on the continuing effort to improve our understanding of the possible relationships between environmental factors and human disease.

Sincerely,

William D. Ruckelshaus
Chairman

Environmental Protection Agency • National Cancer Institute
National Heart, Lung and Blood Institute • National Institute for Occupational Safety and Health
National Institute of Environmental Health Sciences • National Center for Health Statistics
Centers for Disease Control • Food and Drug Administration

PREFACE

Congress established the Task Force on Environmental Cancer and Heart and Lung Disease as a formal mechanism of coordination and cooperation among the U.S. Environmental Protection Agency (EPA), some of the Public Health Service Agencies within the Department of Health and Human Services (DHHS), and other Agencies in an attempt to deal with the complex problem of determining cause-and-effect relationships between environmental pollutants and adverse health effects. The enabling legislation, the Clean Air Act Amendments of 1977 (Public Law 95-95, Section 402), designated the initial member Agencies to be EPA; and from the National Institutes of Health (NIH), the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Environmental Health Sciences (NIEHS); and from the Centers for Disease Control (CDC), the National Institute for Occupational Safety and Health (NIOSH). Other DHHS Agencies that have become official members of the Task Force are the National Center for Health Statistics (NCHS), the Centers for Disease Control, and the Food and Drug Administration (FDA). The Department of Energy (DOE) was granted observer status during 1982 and became a full member in 1983. The Administrator of EPA or a person delegated by the Administrator chairs the Task Force.

In addition to stimulating cooperation among EPA, DHHS, and other Agencies, the Task Force is mandated to recommend research to determine and quantify the relationship between environmental factors and human disease and to recommend strategies, research, and other measures to reduce the risk and prevent environmentally related cancer and heart and lung disease. The Task Force informs Congress annually about its progress in addressing the mandate.

This report describes the accomplishments of the Task Force between September 1982 and August 1983. Chapter 1 introduces the Task Force and its activities within the context of the environmental disease problem. Chapter 2 states the Task Force recommendations to Congress. Chapter 3 is a summary of the findings and recommendations of the Task Force-sponsored Workshop on Environmentally Related Nononcogenic Lung Disease. Chapter 4 summarizes the papers presented at the September 1982 symposium on exposure assessment. Chapter 5 is a status report on the continuing activities of the Task Force Working Group and its project groups.

CONTENTS

Page

EXECUTIVE SUMMARY vii

Chapter 1 INTRODUCTION 1

Chapter 2 RECOMMENDATIONS TO CONGRESS 7

Chapter 3 SUMMARY OF THE WORKSHOP ON ENVIRONMENTALLY RELATED NONONCOGENIC LUNG DISEASE 13

- Background 13
- Organization and Agenda 14
- Overview of Problem 16
- Session on Epidemiology, Statistics, and Risk Assessment 17
- Session on Clinical Research 24
- Session on Basic and Animal Research 28
- Selected References 34
- Participants in the Workshop on Environmentally Related Nononcogenic Lung Disease 37

Chapter 4 SUMMARY OF THE SYMPOSIUM ON EXPOSURE ASSESSMENT: PROBLEMS AND PROSPECTS 39

- Background 39
- Symposium Overview 42
- Agenda for the Symposium on Exposure Assessment: Problems and Prospects 47

Chapter 5 CONTINUING TASK FORCE ACTIVITIES 49

- Working Group 49
- Project Groups 52
  - Exposure and Metabolic Mechanisms 53
  - Interagency Education Program Liaison Group 58
  - Quality Assurance in Analytical Methodology 60

CONTENTS (Concluded)

Appendix A SECTION 402 OF PUBLIC LAW 95-95

Appendix B MEMBERS OF THE TASK FORCE, WORKING GROUP, AND PROJECT GROUPS

Appendix C LIST OF PUBLICATIONS ORIGINATING FROM THE TASK FORCE ON ENVIRONMENTAL CANCER AND HEART AND LUNG DISEASE

Appendix D ENVIRONMENTALLY RELATED NONONCOGENIC LUNG DISEASE WORKSHOP BIBLIOGRAPHY

Appendix E MEETING DATES

EXECUTIVE SUMMARY

The Task Force on Environmental Cancer and Heart and Lung Disease was created by Congress during an era when scientists were increasingly recognizing or at least suspecting that agents in the environment can cause disease. Public awareness of threats to the environment and possible associated health consequences was high. The interagency approach to the study of environment-disease relationships, embodied by the Task Force, has helped to coordinate the use of scientific resources and ensure communication among the participating Agencies.

The activities of the Task Force Working Group and its project groups continue to address various aspects of the environmental disease issue, including the following:

- Role of environmental agents in causation and exacerbation of respiratory diseases
- Mechanisms of toxicity relevant to cancer and heart and lung disease
- Education of health professionals about the causes, incidence, control, and prevention of environmental/occupational disease
- Validation of data through the promotion of quality assurance programs for analytical methodology
- Study of legal and administrative impediments to epidemiologic research.

Both the substantive outcomes of these activities and the cooperation engendered contribute to the study of the relationship between environmental pollution and human disease and to the development of research recommendations aimed at reducing or preventing the incidence of environmentally related disease.

Using workshops as one mechanism for acquiring information, the Task Force this year focused on two areas for indepth study:

1. The relationship between environmental factors and nononcogenic lung disease
2. Assessment of human exposure to environmental pollutants.

Participants at the Task Force-sponsored Workshop on Environmentally Related Nononcogenic Lung Disease identified research needed to reduce or prevent the incidence of lung disease, excluding lung cancer. Three major themes were found to underlie this sizeable group of research needs:

- Longitudinal studies are required to determine the role of the various risk factors in the causation of lung diseases
- The relationship between acute adverse effects on pulmonary function and the development of chronic and irreversible changes in the lung is a key to understanding the effects of environmental and occupational exposures
- Information is required on both exposure concentration and dose of pollutant to tissue for understanding the health effects of airborne pollutants.

It was emphasized by workshop participants that three tools of research--epidemiology, clinical studies, and basic and animal studies--must be used complementally to clarify relationships between environmental factors and nononcogenic lung disease.

The determination of exposure to environmental pollutants was the subject of a second Task Force-sponsored workshop. The scarcity of exposure data and the need to have such data for assessing risk to human health provided the impetus for the organization of the workshop.

Representatives from the regulatory and health Agencies and academia described exposure determination procedures.

Participants enumerated the unique problems associated with determining human exposure to toxic substances in the workplace, in air, water, and soil, in food, and in drugs. Also described were information sources that offer clues about exposure, when, as is frequently the case, exposure cannot be measured directly.

Based on its sixth year activities and continuing concerns from previous years, the Task Force has developed several recommendations to Congress. A recommendation, identified by participants in the Workshop on Environmentally Related Nononcogenic Lung Disease, would require coordinated, committed long-term efforts to yield meaningful results:

- Longitudinal studies of human populations as a basis for quantifying risk factors in the causation and aggravation of a group of lung diseases and for designing cost-effective prevention strategies.

Other recommendations, which reflect continuing concerns from past years, relate to facilitating the conduct of epidemiologic research by relaxing legal and administrative impediments and continuing support to the operation of the National Death Index. Specifically, the Task Force recommends support of

- Legislative proposals to facilitate access to data required in the conduct of epidemiologic studies
- Continuation and improvement of the National Death Index under the auspices of the National Center for Health Statistics.

The Task Force emphasizes the coincident importance of protecting human research subjects and the individual's right to privacy.

The Task Force offers its recommendations and information obtained through its cooperative activities as its contribution to approaching the difficult problem of determining relationships between environmental factors and human disease.

Chapter 1

INTRODUCTION

The Task Force on Environmental Cancer and Heart and Lung Disease was established by Congress through enactment of the Clean Air Act Amendments of 1977 (Section 402 of Public Law 95-95) to promote and formalize cooperation among the U.S. Environmental Protection Agency (EPA), the Department of Health and Human Services (DHHS), and other Agencies. The member Agencies within DHHS are the National Cancer Institute (NCI); the National Heart, Lung, and Blood Institute (NHLBI); the National Institute for Occupational Safety and Health (NIOSH); the National Institute of Environmental Health Sciences (NIEHS); the National Center for Health Statistics (NCHS); Centers for Disease Control (CDC); and the Food and Drug Administration (FDA). The Department of Energy (DOE) became a full member in 1983.

The Task Force is specifically mandated* to

- Recommend a comprehensive research program to determine and quantify the relationship between environmental pollution and human cancer and heart and lung disease
- Recommend comprehensive strategies to reduce or eliminate the risks of cancer or such diseases associated with environmental pollution
- Recommend research and such other measures as may be appropriate to prevent or reduce the incidence of environmentally related cancer and heart and lung diseases
- Coordinate research by, and stimulate cooperation between, the EPA, DHHS, and such other Agencies as may be appropriate to prevent environmentally related cancer and heart and lung diseases

---

* See Appendix A for full text of Section 402(b) P.L. 95-95.

- Report to Congress annually on progress and problems encountered in carrying out this mandate.

The determination of cause-and-effect relationships between environmental pollutants and human disease remains, to a large extent, a difficult problem confronting the entire scientific community. As some part of their mission, each of the Task Force member organizations is individually charged with addressing various aspects of the problem:

- EPA--Determination of the risks to human health of pollutants that are discharged into the environment
- NCI--Identification, classification, and evaluation of environmental carcinogens and tumor promoters; assessment of the relationships between these carcinogens and cancer cause and incidence; and prevention of cancer through research and educational programs
- NHLBI--Study of possible relationships between environmental factors and heart disease and lung disease
- NIOSH--Research on occupational factors related to cancer and respiratory and cardiovascular diseases so as to understand their causes and to detect their vulnerabilities to prevention
- NIEHS--Recognition, identification, and investigation of environmental factors that may have adverse effects on population groups; quantification of effects; and study of the mechanisms of action of toxic agents on biological systems
- NCHS--Collection of health data to furnish basic national health statistics on morbidity and mortality, enabling the selection of populations with potential environmentally related diseases for further study, and monitoring of the effectiveness of public health programs for reducing disease and lowering mortality
- CDC--Investigation of chronic disease occurrence, e.g., cancer, outbreaks of disease, and health risks related to man-made chemical or physical agents and to natural environmental hazards; and response to specific environmental health problems and emergencies as they arise

- FDA--Identification, reduction, and control of hazards associated with foods, drugs, biological products, therapeutic devices and radiological products.

- DOE--Study of potential adverse health effects that may be associated with energy technologies.

When representatives from these member organizations meet together at Task Force meetings, each brings a unique perspective that contributes to the collective understanding of the environmental disease problem. The exchange of information about Agency and Department research programs and the enhanced cooperation engendered by these interpersonal interactions are major achievements of the Task Force, which serve to address one aspect of the Task Force mandate.

Task Force activities during FY83 continued to address the various aspects of the Task Force's mandate. The Task Force Working Group of representatives designated by their respective Agency or Department meet together to plan activities. Information exhange, research coordination, and enhanced cooperation have been functional outgrowths of Working Group meetings. To focus on specific issues in the study of the environment and health, the Working Group establishes activity project groups, subcommittees, and ad hoc committees. During FY83, these subcommittee and project groups included the following:

- Planning Committee for the Workshop on Environmentally Related Nononcogenic Lung Disease

- Planning Committee for the Symposium on Exposure Assessment

- Project Group on Exposure and Metabolic Mechanisms and subcommittees on exposure and metabolism

- Project Group on Quality Assurance in Analytical Methodology
- Interagency Education Program Liaison Group.

Acknowledging the scientific complexity of determining and quantifying the relationship between environmental factors and human disease, the Task Force last year decided to approach the problem through the mechanism of workshops. Accordingly, a major activity of the Task Force's sixth year was the Workshop on Environmentally Related Nononcogenic Lung Disease. Although deaths from chronic obstructive pulmonary disease (includes bronchitis, emphysema, asthma, and other allied conditions) ranked fifth among causes of death in the United States in 1981, and the age-adjusted death rate for chronic obstructive pulmonary disease has shown an upward trend since 1950, relatively little is known about the nononcogenic lung diseases.*

The workshop, held March 13-18, 1983, at the Airlie Conference Center in Airlie, Virginia, brought together experts in the various disciplines related to the study of nononcogenic lung disease. Approximately 40 participants met in intensive working sessions to discuss issues and draft a document defining research needs, directions, and strategies as they pertain to lung disease and the environment in the broad areas of epidemiology, statistics, and risk assessment; clinical research; and basic and animal research. Chapter 3 of this report contains a summary report on this workshop, including the research needs identified by workshop participants. The findings of this workshop should serve as a contribution both to the scientific knowledge and as background to Government research planning activities.

---

* National Center for Health Statistics. Annual Summary of Births, Deaths, Marriages, and Divorces: United States, 1981. Monthly Vital Statistics Report. Vol. 30, No. 13. DHHS Publ. No. (PHS)83-1120. Public Health Service. Hyattsville, Maryland. December 1982.

Another important Task Force activity was the sponsorship, with the Scientific Liaison Staff of the Food and Drug Administration, of a symposium entitled "Exposure Assessment: Problems and Prospects." The symposium was held September 13-14, 1982, at the National Institutes of Health and included participants from Federal Agencies and non-Government institutions, who reviewed various methods of determining human or environmental exposure to toxic substances. The determination and measurement of exposure are important aspects of the problem of establishing relationships between environmental pollutants and adverse health effects. The papers presented at the symposium have been collected and reviewed and will be published in the Journal of Clinical Toxicology in early February 1984. Chapter 4 of this report is a brief summary of the papers presented.

Chapter 5 summarizes the other activities of the Task Force Working Group and project groups. An integral aspect of the Task Force mandate is the formulation of recommendations for research. The recommendations submitted in this report (Chapter 2) derive from the activities and continuing concerns of the Task Force.

Chapter 2

RECOMMENDATIONS TO CONGRESS

The Task Force on Environmental Cancer and Heart and Lung Disease is mandated to recommend strategies and other measures to determine and quantify environmental pollution-disease relationships and to prevent or reduce the incidence of environmentally related diseases. To help identify risk factors relevant to the understanding of certain diseases, participants at the Task Force Workshop on Environmentally Related Nononcogenic Lung Disease recommended increased emphasis on longitudinal studies of human populations. Other recommendations submitted to Congress this year represent continuations of concerns from previous years pertaining to legal and administrative impediments to epidemiologic research and continued support for the National Death Index.

Recommendation 1:

> Longitudinal studies of human populations, which could provide a basis for better quantification of risk factors in the causation and aggravation of an important group of lung diseases (including the chronic obstructive pulmonary diseases), should be supported. Such information is essential to the design of cost-effective preventive strategies.

Although clinical investigations as well as basic research provide much valuable information, the well-designed epidemiologic study produces the strongest evidence of effects of environmental factors on human health. It is becoming increasingly clear that the most informative epidemiologic

Preceding page blank

studies are prospective, long-term studies, in which a range of environmental factors can be accurately quantified, and in which adverse health effects in individuals can be studied against a background of normal growth, development, and senescence, and in which there is sufficient control of confounding variables. Such studies may describe the "natural history" of a disease, provide opportunities for intervention, and provide valuable opportunities to study in detail the acute responses to environmental factors in subjects under long-term observation.

The recent Airlie House Workshop on nononcogenic lung disease recommended these kinds of epidemiologic-clinical studies, as have numerous previous task forces and workshops. Two reports that address many of the specific benefits and problems of such studies are the Epidemiology of Respiratory Diseases Task Force Report (July 1979, Lung Division, NHLBI) and the Human Health and the Environment Task Force Report (1977, NIEHS). Such epidemiologic studies require a high level of organization and commitment by sponsors who recognize the unique benefit to be obtained.

Recommendation 2:

> Legislative proposals should be supported that would facilitate access to data required in the conduct of epidemiologic studies.

The Task Force's Fourth (1981) and Fifth (1982) Annual Reports to Congress contained recommendations to minimize or remove legal impediments to epidemiologic research. These impediments are still in place and impair access to data on individuals. Epidemiologists require such data to establish disease etiologies.

A wealth of information that would be valuable to epidemiologic research is now collected by many Federal Agencies. Some of these Agencies and their relevant data collections are

- National Center for Health Statistics
  - Health and demographic surveys
  - Health manpower inventories and surveys
  - National Vital Statistics Systems
  - Health resources utilization statistics
  - National Death Index
- National Cancer Institute
  - Surveillance, Epidemiology and End Results (SEER) data base of cancer incidence, survival, and mortality on approximately 10 percent of the population
- Centers for Disease Control/National Institute for Occupational Safety and Health
  - NIOSH National Occupational Exposure Survey (NOES)
  - NIOSH periodic studies of particular industrial processes
  - NIOSH National Surveillance Network
- Social Security Administration
  - 1 percent continuous work-history sample (CWHS)
  - Industry quarterly earnings reports by employee
  - Disability Insurance Fund
  - Numident File created from Social Security Number (SSN) Applications (Form SS5)
- Census Bureau, Department of Commerce
  - 1980 Census of Population "long form" used for about 20 percent of the population
  - Current Population Survey (CPS) obtained each year
  - Post Enumeration Survey (PES) for the 1980 census

- Internal Revenue Service
  - Form 1040 of Individual Taxpayer Returns
  - Forms W-2, W-2p, and 1099 from Employers
  - Statistics of Income (SOI) sample
- Bureau of Labor Statistics, Department of Labor
  - Health and safety statistics
  - Day-to-day logs of occupational illness and injury
- U.S. Department of Agriculture
  - Pesticide surveys
  - Nutrition surveys
- Health Care Financing Administration
  - Medicare Application File
  - Medicare Payments File
  - Medicaid Summary File
- Veterans Administration and Department of Defense
  - Retired military and disabled veterans health care records
  - Retired military and disabled veterans mortality records
  - Mortality records for 95 percent of all wartime active duty persons.

Linkage of such record systems would contribute to epidemiologic studies of disease risk factors and the natural history and prognosis of disease.

While the value of these data and of the linkage of data systems is recognized, considerations of confidentiality and individual privacy also require attention. Access to individually identifiable data should only be available to researchers whose protocols are consistent with applicable laws and regulations and have been approved by Institutional Review Boards (IRB). IRB approval requires incorporation of personal data confidentiality and informed consent provisions into the protocol. Measures should also be included to ensure the protection of human research subjects.

Proposals to relax impediments to approved epidemiologic research might include, for example, the following provisions:

- Access to Social Security Administration quarterly earnings records to obtain individual occupation and industry information, employer identification numbers, and individual linkage data for subject identification
- Access to the Internal Revenue Service Master File for last known filing address and date of filing
- Assurance of continued support for the National Death Index under the auspices of the National Center for Health Statistics (see Recommendation 3).

It might be appropriate for one Agency to serve as a clearinghouse for access to Federal data collections. Other Federal Agencies could go through the clearinghouse to obtain data required in their epidemiologic studies, and the clearinghouse would be entrusted with protecting the confidentiality of the data and the individual's right to privacy.

Recommendation 3:

> The National Death Index, implemented and maintained by NCHS, should be supported to ensure its long-term continuation and improvement.

The National Death Index, described in detail in the Task Force's Fifth Annual Report to Congress (1982), is an important epidemiologic research tool. This central, computerized index of death record information assists investigators in determining whether persons in their studies may have died, and if so, provides the names of the states in which those deaths occurred and the corresponding death certificate numbers. The investigator is then able to purchase copies of the death certificates from the appropriate state vital statistics offices and to obtain specific statistical information such as cause of death. Before implementation of the National Death Index, investigators often had to search the vital statistics records of all or most states to ascertain whether a death certificate had been filed for any individual in the entire study group. This process was very costly and time-consuming.

The National Death Index file is compiled from magnetic tapes submitted under contractual arrangement to the National Center for Health Statistics by the state vital statistics offices. The file begins with deaths occurring in 1979 and is updated annually. The importance of this epidemiologic data base will continue to increase as subsequent years of death are added to the file. Adequate funding to cover the costs of updating the file and for further development of computerized matching techniques will be an important factor toward the effective use of this new service.

Chapter 3

SUMMARY OF THE WORKSHOP ON ENVIRONMENTALLY RELATED NONONCOGENIC LUNG DISEASE

BACKGROUND

As an appropriate way to address its mandate, the Task Force decided in 1982 to conduct a series of workshops on specific disease problems. Environmentally related nononcogenic lung disease was chosen as the subject for the first workshop, the purpose of which was to determine the research needed to minimize or prevent lung disease other than cancer. Lung cancer and the effects of cigarette smoking per se were excluded from primary consideration in this workshop because of the enormity of those problems in and of themselves. It is well accepted and worth emphasizing that cigarette smoking is the major cause of lung disease. (The Task Force is planning a separate workshop on lung cancer in FY84.)

The urgency of improving understanding of nononcogenic lung disease is emphasized by the fact that a portion of the lung diseases, the chronic obstructive pulmonary diseases (COPD), constitute the fifth leading cause of death in the United States, surpassed only by heart disease, cancer, stroke, and accidents.* Major lung diseases within the COPD include asthma, bronchitis, and emphysema, which received the main emphasis at the workshop.

The Workshop on Environmentally Related Nononcogenic Lung Disease, held March 13-18, 1983, at Airlie House Conference Center in Airlie, Virginia, was the culmination of many months of planning by an organizing committee.

---

* National Center for Health Statistics, Annual Summary of Births, Deaths, Marriages and Divorces: United States, 1981. Monthly Vital Statistics Report. Vol. 30, No. 13. DHHS Publ. No. (PHS) 83-1120, Public Health Service, Hyattsville, Maryland. December 1982.

ORGANIZATION AND AGENDA

Instead of commissioning status papers on major topics of interest, it was decided that the Workshop be devoted almost exclusively to group discussions, out of which recommendations for research would be developed. To provide focus for the group discussions, several preliminary steps were taken.

The first was establishing the scope of the effort by identifying major areas of expertise and specific individuals from those disciplines who were widely recognized for their contributions to research in pulmonary biology and pulmonary disease. The areas ranged from molecular biology to epidemiology and statistics, and it was thought that such individuals could best identify research priorities and current and near-term research needs. The selection of participants was based on scientific reputation. For practical reasons, the number was limited to 37 participants from the United States and Canada. (Participants are listed at the end of this chapter.) Although the workshop participants were assigned primarily to one of the three sessions, interactions among the groups were actively encouraged.

The format of the workshop was developed to provide flexibility for its participants to comprehensively address lung disease problems. Through preworkshop sessions and activities, the Workshop Planning Committee sought to involve the participants in the design of the agenda. Before the Workshop, participants were asked to prepare a list of major questions, information gaps, and unresolved issues related to nononcogenic lung diseases. The Committee then selected 61 statements from the responses and asked the participants to assign a relative priority to each. The participants were also asked to identify two or three topics that they considered to be of highest priority and provide written comments on them. These comments provided the background material on which the workshop discussions were based and from which the statements of research needs were eventually derived.

The participants were divided into three working groups according to subject matter: Epidemiology, Statistics, and Risk Assessment; Clinical Research; and Basic and Animal Research. Membership in the groups was diversified by discipline, both to promote cross-fertilization and to acknowledge that some disciplines are essential to all research areas. Intergroup discussions were promoted to the extent possible.

The agenda included short plenary sessions on the first and third days and a longer plenary session on the fourth morning, at which session chairpersons gave summary reports, primarily for representatives of the Task Force member Agencies.

After the workshop, the chairpersons synthesized and edited the material to produce a cohesive technical report, which will be submitted for publication to a peer-reviewed journal in the winter of 1983-1984.

OVERVIEW OF PROBLEM

Mortality from respiratory diseases (excluding cancer) has been increasing generally since 1950. The greatest rise has been shown by emphysema and chronic obstructive lung disease, for which the age-adjusted death rate rose from 4.9 per 100,000 population in 1960 to 14.7 in 1977.[1]

Illness from respiratory disease, excluding lung cancer, has been estimated by surveys of the National Center for Health Statistics. In 1970, there were an estimated 13,800,000 persons with chronic bronchitis, emphysema, or asthma--the three major components of chronic obstructive pulmonary disease.[2] In 1981, this figure had risen to an estimated 17 million.[3]

The economic cost to the nation of respiratory diseases was estimated at $19.7 billion in FY75. The direct personal health care expenditures for respiratory diseases in 1975 were estimated at $7.6 billion, while the indirect costs from morbidity and mortality from respiratory disease were estimated at $8.5 billion and $3.6 billion, respectively.[4]

The relationship of environmental factors to respiratory diseases has been extensively studied in the past 25 years, with focus on tobacco smoking, occupational exposures, indoor and outdoor air pollution, genetic factors, and the "natural history" of respiratory diseases. These studies--epidemiologic, clinical, and experimental--have provided important information and at the same time have served to point out serious gaps in the knowledge about the relationship between the environment and respiratory disease. Consequently, the Workshop participants at the Airlie conference highlighted additional research needed in epidemiology, clinical studies, and basic and animal studies. These research needs will be presented to the Task Force member Agencies for their review and consideration.

---

[1] Klebba, Joan. Mortality from Diseases Associated with Smoking: United States, 1960-77. Vital and Health Statistics, Series 20, No. 17, NCHS, Hyattsville, Maryland. January 1982. Table 8, p. 56.

[2] Wilder, C.S. Prevalence of Selected Chronic Respiratory Conditions, United States, 1970. Series 10 No. 84 NCHS, Rockville, Maryland. September 1973. Table A, p. 4.

[3] Unpublished data from the National Health Interview Survey, National Center for Health Statistics.

[4] NHLBI. Report of Task Force on Epidemiology of Respiratory Diseases. July 1979. NIH Pub. No. 82-2019. November 1981.

SESSION ON EPIDEMIOLOGY, STATISTICS, AND RISK ASSESSMENT

Epidemiologic studies have provided suggestive evidence about the specific effects of aging, occupation, and general environmental exposures, as well as cigarette smoking, on respiratory diseases. There is no question that in the middle of this century there were excesses of respiratory sickness and death during episodes of severe pollution associated with burning of fossil fuels. However, the extent to which acute air pollution episodes or long-term exposure to lower pollution levels were factors in causing new cases of lung disease remains unclear.

Part of the problem relates to the nature of these lung diseases and to shortcomings of the methods used to study them. Because these diseases usually develop slowly over long time periods, it is often difficult to determine when they began. The roles of several risk factors, including cigarette smoking (which is considered the most powerful factor), occupational exposure, events in early life, and outdoor and indoor exposure to air pollutants, remain poorly quantified.

Each of the three working groups independently concluded that more longitudinal studies are required to unravel the complex interrelationships among these risk factors. Some of these longitudinal studies would require complex multidisciplinary and expensive strategies. Others, with more limited goals, will probably still require highly organized arrangements for long-term followup. The workshop participants agreed that several years of committed effort will be necessary to produce meaningful results.

Suggested Topics for Longitudinal Studies

While recognizing the difficulties of establishing cohorts for long-term followup, the workshop participants recommended the conduct of longitudinal studies involving children. Such studies are critical to an understanding of the natural history of obstructive airway disease and provide opportunities to quantify risk factors, such as maternal smoking, air pollution, and acute respiratory illness during the first 5 years of life.

Long-term studies of adults, intended to determine long-term risks of exposure to various toxic chemicals and dusts, generally lack sufficient numbers of subjects with any particular occupational or environmental exposure. These data are needed as the basis for developing dose-response curves, which are essential to estimations of risk.

The workshop participants recommended longitudinal studies in adults as a way of investigating the long-term significance of early changes in small airway function. New methods should be standardized for this purpose, to supplement the well-established expiratory flow methods. Information from such studies would help to characterize the high-risk individual, who is expected to progress to clinically apparent airway obstruction. Participants agreed that additional study is needed on whether early intervention in the course of the development of COPD can modify its course.

Long-term studies of various occupational groups would provide information about the risk of exposure to a variety of inorganic and organic dusts. Information is required for a better understanding of the mechanisms and role of immunologic responses, the relationship between acute symptomatology and the development of chronic disease, and the preventive value of preplacement testing and surveillance. Specific diseases that would benefit from longitudinal studies include occupationally induced asthma, byssinosis, and inorganic dust diseases, including asbestosis, silicosis, and coal workers' pneumoconiosis. Information from such studies would contribute to the development of preventive measures and therapeutic interventions.

Accurate assessment of the risk to public health from exposure to air pollution requires estimating the health responses over a range of exposure levels and periods. The concentrations of air pollutants in American cities may be associated with a risk too small to measure adequately by epidemiologic studies, yet these pollutants may still pose an important public health problem when the exposed population is large. In these cases, the workshop participants suggested studying specific occupational groups or populations in countries where the concentration of pollutants is known to be high enough to develop dose-response data.

The long-term effects of brief high-level exposures to toxic chemicals are not well understood. Details of the chemical composition of the presumed agent and the intensity of the exposure are often not known. Studies would be useful to describe the distribution and occurrence of acute inhalation disorders in general and high-risk groups, such as firefighters, and the long-term consequences on the respiratory system.

Some key research needs related to longitudinal studies were identified by the workshop participants:

a. Effects of pollutant exposures from both indoor and outdoor sources on the growth and development of children's lungs should be studied.

b. In adults, studies are needed to determine the effect of specific environmental exposures on the rate of change in lung function and to identify the determinants of individual susceptibility.

c. Occupational exposure studies should include

   1) Natural history of occupationally-induced asthma with emphasis on effects of intermittent exposures

   2) Assessment of risk factors in the development of byssinosis in workers chronically exposed to textile dusts

   3) Identification of workers exposed to inorganic dusts (including asbestos, silica, and coal dust) who are in transition from acute to chronic disease

   4) Clarification of the relationship among antibody titers, exposure levels, and severity of lung disease related to organic dusts

   5) Conduct of both cross sectional and longitudinal epidemiologic studies when highly-exposed groups can be identified (may require international collaboration)

   6) Evaluation of pre-employment tests and surveillance methods related to occupational exposures.

Other Suggested Epidemiologic Studies

The workshop participants suggested their perceived needs for epidemiologic research other than longitudinal studies. Some of these research needs relate to data collection and recordkeeping and the application of an imaginative integration of disciplines to the study of nononcogenic lung diseases.

The participants noted the value of data collected through autopsies and suggested the voluntary autopsy program that now exists in the United States for underground coalminers be extended to other occupational groups. The inaccuracy of death certificates was also discussed as a significant problem, and it was suggested that the cause of death listed on the death certificate be compared with clinical or autopsy diagnoses for specific occupational diseases and for specific causes of death.

The development of a National Death Index (NDI) by the National Center for Health Statistics heightens the need to improve the accuracy of death certificates. The NDI provides a unique centralized resource but is only as good as the data supplied to it. The participants recommended the development of approaches to improve standards of reporting with emphasis on accuracy of diagnosis and careful monitoring of the approaches over several years to determine their effectiveness.

Combined epidemiologic-morphologic-mineralogic studies were suggested to detect changes in human lungs from exposure to defined types and levels of gaseous and particulate air pollutants. Short-term studies of the effects of air pollutants on sensitive individuals were recommended on the basis of findings that persons with asthma may experience transient changes in airway resistance from exposure to levels of pollutants commonly encountered in the community; subjects for such studies would have to be selected from well-characterized population-based samples rather than from volunteer groups.

The workshop gave some consideration to exposure to pollutants through routes other than inhalation. The recent identification of bisulfite as a cause of asthma when ingested in wine and vegetables prompted suggestion of a study of food additives.

The suggested research needs for epidemiologic studies, other than longitudinal studies, included the following:

a. Voluntary autopsy programs (similar to that established under the Federal Coal Mine Health and Safety Act of 1969 for coal miners) should be established for selected occupational groups.

b. Studies should be initiated to define precisely those morphologic changes in lungs of human populations exposed to definite types and levels of gaseous and particulate air pollutants.

c. Studies are needed to determine the accuracy (and sources of inaccuracy) of death certificate reporting of occupational lung diseases. Pilot studies should be done on methods of improving the quality of death certificate reporting.

d. Studies should be done on the short-term effects of exposure to air pollutants on persons with acute sensitivity. Such populations include persons with asthma, chronic bronchitis, or emphysema.

Statistics and Risk Assessment

In proposing various research initiatives, the workshop participants also recognized a need for the development and use of innovative statistical methods and alternative study designs. Despite the repeated emphasis on longitudinal studies, it was acknowledged that not only was an optimal design for such studies not clear but also there were complex logistic, administrative, and financial difficulties in mounting such studies.

The workshop participants recognized a need to develop better statistical methods to characterize patterns of air pollutant distribution and to estimate personal exposures. Risk assessment was acknowledged as an important technique in relating environmental exposures to human disease. Such problems as extrapolation to low doses, relationship of animal data to human risk, and statistical bias require further development of statistical methods.

Identified research needs in the areas of statistics and risk assessment included the following:

a. Statistical research should be done to develop specific strategies for the design, conduct, and analysis of longitudinal studies to help characterize life time patterns of pulmonary functions and identify risk factors modifying those patterns.

b. Statistical research is required to develop sampling strategies for monitoring air pollutants and to develop techniques for estimating personal exposure to air pollutants.

c. To improve the value of risk assessment techniques in nononcogenic lung disease, it is necessary to obtain not only specific measurements in humans but also to use mechanistic studies to predict the shape of the dose-response relationship at low levels of exposure.

d. Methodologic studies are needed to obtain valid estimates of uncertainty in risk assessment procedures.

SESSION ON CLINICAL RESEARCH

Over the past 20 years, various means have been developed for the detection of the clinical effects of environmental agents. A relatively simple test of lung function, the forced expiratory volume in one second (FEV_1), has yielded information on short- and long-term effects of air pollutants. This single test of lung function has been very useful but does not measure all possible effects of environmental agents on pulmonary function.

Therefore, the workshop participants identified a need for improved tests and new noninvasive methods for testing lung function. These new and improved methods could include

- Simple methods of determining aerosol deposition in the lung and clearance capability for use in field studies
- Noninvasive methods of measuring lung elasticity and for measuring excessive accumulation of mucus
- Methods of measuring lung ventilation rates without the use of face masks or mouthpieces in the work area
- Portable laboratories to measure lung function that are suitable for temporary location in a workplace.

These methods would require clinical evaluation and testing before being implemented in the field.

The participants noted that the availability of lung function tests and their use as part of pre-placement testing, together with the development of schemes for the surveillance of lung function in different industries, have outpaced the critical review of the value and need of these methods.

Therefore, the participants suggested a review to determine how preplacement tests should be used, if at all, as well as the type of test and its frequency of use in different industries. The question of how to interpret the results of these tests in relation to long-term adverse effects also remains unanswered.

The clinical laboratory and exposure chamber were also discussed as important means of acquiring information about the short-term effects of exposure to pollutants. While these require careful standardization and sometimes the use of elaborate equipment, short-term laboratory studies can be accomplished without such complex facilities. The workshop participants identified a number of areas in which less sophisticated but well-designed studies are needed. These include

- Studies of hyperreactivity and "adaptation" to pollutants
- Studies of interaction among different pollutants and between infectious agents and pollutants
- Exercise studies of patients with lung disease due to occupational pollutants to clarify limitations of functions
- Studies of individuals with specific sensitivity to different pollutants to determine if bronchial irritation is related to increased sensitivity to dusts and gases.

There was also discussion of the possibility that animal studies may reveal certain tests that could be used as markers or indicators of adverse effects due to exposure to toxic substances. These could lead to clinical investigations in humans and the development of tests that can be used in the field and that may provide earlier indication of adverse effects than tests currently available.

To obtain needed information on clinically detecting the effects of exposure, the workshop participants suggested the following research needs:

a. New non-invasive methods for studying the effects of environmental agents on human lung function should be developed.

b. Studies are needed on the value of preplacement testing, therapeutic intervention, and long-term follow-up in different industries.

c. Clinical laboratory studies of changes in the lung due to environmental factors and studies of patients with lung changes due to occupational factors should be developed and expanded.

d. Closer working relationships between toxicologists and occupational health physicians should be encouraged as a means for obtaining early discovery of possible new approaches to the detection of biochemical effects of exposure to harmful substances in the work area or in the general environment.

Identification of Environmentally Related Diseases

In discussing the ways in which a disease caused by environmental exposure is first discovered, workshop participants agreed that often the first significant observation is made by a physician who notices an unusual occurrence of illness or pathology, usually related to occupational exposure. Recent examples include the recognition of the toxicity of Kepone, the association of lung cancer with occupational exposure to bischloromethyl ether (BCME) in young workers, and the identification of a rare liver cancer in workers exposed to vinyl chloride.

Similar instances may have been overlooked because the physician was unable to follow up leads or had no one to call on for assistance. Therefore, participants identified a need for exploratory studies to develop methods to help physicians recognize environmental factors in disease etiology. The state medical societies might be the first point of contact, with Federal investigators from CDC or NIOSH involved as the next step.

The workshop participants recommended the initiation of a pilot study on this issue:

- A pilot study should be launched to determine whether formal channels of consultative advice should be made available to physicians in the field for the identification of illness due to exposure to environmental pollutants.

Treatment of Environmentally Related Nononcogenic Lung Disease

Participants addressed the issue of adequate treatment for persons who have developed environmentally related nononcogenic lung disease. Although there have been controlled studies of the effectiveness of different treatments of asthma and diffuse interstitial fibrosis of various types, there are only a few studies of the results of treatment of occupational asthma, allergic alveolitis, early silicosis, or even chronic byssinosis. Such studies could be conducted in those areas where these diseases occur very frequently. Workshop participants expressed a need for well-designed, randomized clinical trials to evaluate the effectiveness of proposed treatments.

The following research need was proposed:

- Clinical trials of different forms of treatment of existing occupational lung disease should be conducted to provide guidance to the many physicians who see only a few such cases and lack information on the effectiveness of different treatments.

SESSION ON BASIC AND ANIMAL RESEARCH

As with the Epidemiologic and Clinical Research Sessions, the participants in the Basic and Animal Research Session acknowledged that interactions among the multiple approaches to the study of pulmonary disease and the role of environmental factors in its etiology are important. However, the primary emphasis in these sessions was on basic pulmonary biology, mechanisms of injury and repair, measurements of environmental exposure and dose, and development of animal models. Measurement of exposure and dose is fundamentally important in epidemiologic studies, as well as laboratory studies.

Evaluation of Exposure and Dose to Tissue

Workshop participants discussed the need for improved instrumentation and methods to

- Characterize atmospheres according to particle aerodynamic size, morphometry, and chemical composition
- Measure ventilation patterns in subjects performing various levels of activities.

The need for portable, non-invasive, and relatively simple instrumentation was emphasized.

Information about deposition and clearance of particles and gases in the human lung has largely been obtained in a laboratory setting. The deposition and clearance of inhaled particles and gases in several animal species and humans should be studied to provide better information about the basic mechanisms responsible. Results of such research will aid in the development of risk assessment methodology for inhaled particulates.

Workshop participants identified the following research needs as important to the study of exposure and dose:

a. Study is needed to determine how the chemical and physical characteristics of particles affect clearance from the respiratory tract.

b. Techniques should be developed for estimating the dose of inhaled particles and gases to critical sites within the respiratory tract. Studies should be designed to cover various stages of animal growth and development, as well as later stages of maturity.

Basic Biology of the Respiratory Tract

Similarities and differences among animals, as well as between animals and humans, must be understood to select the most appropriate animal models, to interpret experimental results, and to extend those results to humans. During the past 10 years, significant advances have been made in our understanding of basic biological processes through the development of new methods in molecular and cellular biology. Workshop participants emphasized the value of applying these techniques to studies of environmentally related lung disease.

Although much has been learned about the development of the lungs in humans and animals, participants agreed that much additional study of the biology of lung growth and development would be fruitful. Studies are needed to examine the extent to which immature lungs might be more sensitive to environmental pollutants.

The identified research needs related to basic biology of the respiratory tract included the following:

a. The basic biology of the respiratory system for humans and laboratory animals needs to be studied to permit a more appropriate choice of animal models, as well as more accurate interpretation of data on the effects of pollutants.

b. Studies are needed in laboratory animals of the intracellular, molecular, and genetic events that contribute to the development of respiratory disease as a result of environmental exposures.

c. The factors controlling normal lung development and growth in humans and animals should be identified, as well as alterations of growth by environmental factors.

Development of Respiratory Disease from Air Pollution

Limited information exists about the mechanisms by which pollutants may induce respiratory disease. The Airlie conference underlined the importance of studies with macromolecular, cell, tissue, organ, and whole animal systems to acquire information about the pathogenesis of lung disease.

Workshop participants identified a need for the development of additional biochemical, cellular, and immunologic markers for use as clinical and epidemiologic tools. Development of biological markers will largely be accomplished through the use of laboratory animal models of human lung diseases.

The influence of childhood respiratory infections and possible interactions with environmental pollutants on the growth and development of the lung are not well understood. Workshop participants suggested the use of animal models to study tissue changes and long-term alteration of lung function in relation to respiratory infections.

Several inhaled gaseous pollutants, including ozone and nitrogen dioxide, are suspected of causing COPD if exposures are sufficiently long or severe. Factors that determine whether acute bronchiolitis, for example, is followed by adaptation or progresses to chronic disease are not well understood. Animal studies will help to predict human response at various exposure levels.

Longitudinal studies of laboratory animals exposed at various levels to individual pollutants and mixtures of pollutants are an important part of the overall strategy to understand nononcogenic responses to air pollutants. As noted earlier in the discussion of human studies, the use of longitudinal observations allows investigation of the significance of early changes in the later development of overt disease, such as COPD.

Workshop participants suggested the following as among the research needs in the study of the development of lung disease:

a. Laboratory methods should be developed to identify cellular, molecular, or immunological markers that might aid in detection, prognosis, and treatment of respiratory disease.

b. The mechanisms should be investigated by which environmental pollutants, interacting with infectious agents, may produce lung disease in growing and developing animals and humans.

c. Studies are needed to help determine factors that influence progression of acute bronchiolitis to chronic obstructive pulmonary disease in laboratory animals.

Factors Involved in the Development of Some Specific Respiratory Diseases

Although the effects of cigarette smoking were, by intention, not emphasized in this workshop, cigarette smoking was necessarily recognized as one of the most important factors to consider in studies of lung diseases caused by environmental pollution. Cigarette smoking is also a major factor in studies of occupational lung disease and is a major cause of COPD, especially emphysema. Workshop participants agreed that continuing efforts are essential to differentiate the effects of smoking from the effects of other environmental pollutants.

Recent advances in basic science have indicated a biochemical link between oxidation of a proteolytic enzyme inhibitor and the development of emphysema-like lesions in experimental animals. Participants suggested that animal studies be performed to test the oxidizing ability of inhaled air pollutants to determine whether this measure may accurately predict the occurrence of tissue injury leading to emphysema.

Immunologic lung disease, notably hypersensitivity pneumonitis and asthma, appear to be caused by the inhalation of various dusts or chemical vapors. Animal models of hypersensitivity pneumonitis have been developed, and workshop participants noted their potential importance in the verification of diagnostic tests and development of effective treatment.

Good animal models also exist for studying the effects of exposure to silica and asbestos, and the effects of inhaling dusts have been found to be essentially the same in animals and humans. The size of the particles determines the type of cell they reach, but the chemical nature of the particles is likely to cause their toxic effects. Participants recommended additional study of the mechanisms that produce these toxic effects and further studies of specific diseases such as the pneumoconioses. Furthermore, additive or synergistic effects of various toxic pollutants, in both gaseous and particulate form, may be important in the development of pneumoconioses.

Workshop participants suggested the following basic research needs as important to the understanding of specific lung diseases:

a. Animal models of cigarette smoking should be developed that accurately mimic human responses so that smoking could be studied as a cofactor in environmental lung disease.

b. Animal studies are needed to help determine whether the oxidizing capability of air pollutants tends to predict their potential for inducing emphysema.

c. Basic mechanisms need to be explored by animal studies in immunologic lung disease, such as hypersensitivity pneumonitis and asthma.

d. Laboratory studies are required for determining the causes and mode of development of pneumoconioses.

e. Animal studies are needed to determine additive effects when the lung is exposed to toxic particles in combination with microorganisms, pre-existing lung disease, or cigarette smoking.

Facilitating Mechanisms

Because the study of respiratory disease induced by environmental factors requires collaboration from several disciplines, workshop participants suggested the following mechanism for facilitating research:

- Extensive planning is needed to develop and nurture approaches that will facilitate interactions among scientists from various disciplines and more effectively use the unique facilities and populations (both laboratory animals and humans) that are necessary to improve our understanding of the role of environmental factors in producing respiratory disease.

SELECTED REFERENCES*

Epidemiology, Statistics, and Risk Assessment

Beck, G.J., Schachter, E.N., Maunder, L.R., and Schilling, R.S.F. 1982. A prospective study of chronic lung disease in cotton textile workers. Ann. Intern. Med. 97:645-51.

Black, L.F. 1982. Early diagnosis of chronic obstructive pulmonary disease. Mayo Clinic Proc. 57:765-72.

Commission on Professional and Hospital Activities (CPHA) and IMS America, Ltd. 1977. The hospital record study. Ann Arbor, MI:CPHA.

Dockery, D.W., and Spengler, J.D. 1981. Personal exposure to respirable particulates and sulfates. J. Air. Pollut. Control Assoc. 31:153-59.

Ferris, B.G., Jr., Speizer, F.E., Spengler, J.D., Dockery, D.W., Bishop, Y.M.M., Wolfson, M., and Humble, C. 1979. Effects of sulfur oxide and respirable particles on human health: Methodology and demography of populations in study. Am. Rev. Respir. Dis. 120:767-79.

Fletcher, C., Peto, R., Tinker, C., and Speizer, F.E. 1976. The natural history of chronic bronchitis and emphysema. Oxford:Oxford University Press.

National Academy of Sciences. 1982. Byssinosis--clinical and research issues. Washington, D.C.:National Academy Press.

Parkes, W.R. 1982. Occupational lung disorders, 2nd ed. London:Butterworths.

Speizer, F.E., and Tager, I.B. 1979. Epidemiology of chronic mucus hypersecretion and obstructive airways disease. Epidemiol. Rev. 1:124-42.

Thurlbeck, M.M. 1976. Chronic airflow obstruction in lung disease. Major problems in pathology series, Vol. 5. Philadelphia:W.B. Saunders Co.

---

* See Appendix D for a more extensive listing of references cited by workshop participants in the preparation of background materials and research needs.

Clinical Research

Barter, C.E., and Campbell, A.H. 1976. Relationship of constitutional factors and cigarette smoking to decrease in 1-second forced expiratory volume. Am. Rev. Respir. Dis. 113:305-14.

Chan-Yeung, M., Lam, S., and Koener, S. 1982. Clinical features and natural history of occupational asthma due to western red cedar (Thuja plicata). Am. J. Med. 72:411-15.

Ferris, B.G., Jr., Speizer, F.E., and Ware, J.H. 1981. Uses of tests of pulmonary function to measure effect of air pollutants. In Measurement of risks, ed. G.G. Berg and H. D. Maillie. New York and London:Plenum Press. pp. 211-30.

Gardner, D.E. 1980. Influence of exposure patterns of nitrogen dioxide on susceptibility to infectious respiratory disease. In Nitrogen oxides and their effects on health, ed. S.D. Lee. Ann Arbor, MI:Ann Arbor Science Publishers. pp. 267-88.

Hazucha, M., Silverman, F., Parent, C., Field, S., and Bates, D.V. 1973. Pulmonary function in man after short-term exposure to ozone. Arch. Environ. Health 27:183-88.

Holland, W.W., and Reid, D.D. 1965. Urban factor in chronic bronchitis. Lancet (Feb. 27):445-48.

Karol, M.H. 1981. Survey of industrial workers for antibodies to toluene diisocyanate. J. Occup. Med. 23:741-47.

Kleinman, M.T., Bailey, R.M., Chang, Y.T., Clark, K.W., Jones, M.P., Linn, W.S., and Hackney, J.D. 1981. Exposures of human volunteers to a controlled atmospheric mixture of ozone, sulfur dioxide, and sulfuric acid. Am. Ind. Hyg. Assoc. J. 42:61-69.

Love, R.G., and Miller, B.G. 1982. Longitudinal study of lung function in coalminers. Thorax 37:193-97.

Wegman, D.H., Peters, J.M., Pagnotto, L., and Fine, L.J. 1977. Chronic pulmonary function loss from exposure to toluene diisocyanate. Br. J. Ind. Med. 34:196-200.

Basic and Animal Research

Brody, A.R., and Roe, M.W. 1983. Deposition pattern of inorganic particles at the alveolar level in the lungs of rats and mice. Am. Rev. Respir. Dis. 128(4):724-29.

Clyde, W.A., Jr. 1980. Experimental models for study of common respiratory viruses. Environ. Health Perspect. 35:107-12.

Dalbey, W.E., Nettesheim, P., Griesemer, R., Caton, J.E., and Guerin, M.R. 1980. Chronic inhalation of cigarette smoke by Fischer-344 rats. J. Natl. Cancer Inst. 64:383-90.

Institute of Laboratory Animal Resources, National Research Council. 1981. Animal models for age-related diseases of man--emphysema and chronic bronchitis. In Animal models for research on aging, ed. D. Greenhouse. Washington, D.C.:National Academy Press. pp. 365-76.

Karlinsky, J.B., and Snider, G.L. 1978. Animal models of emphysema. Am. Rev. Respir. Dis. 117:1109-33.

Lee, L.Y., Bleecker, E.R., and Nadel, J.A. 1977. Effect of ozone on bronchomotor response to inhaled histamine aerosol in dogs. J. Appl. Physiol. 43:626-31.

Mauderly, J.L., and Hahn, F.F. 1982. The effects of age on lung function and structure of adult animals. In Advances in veterinary science and comparative medicine. Vol. 26: Respiratory system, ed. D.L. Dungworth. New York:Academic Press. pp. 35-77.

Patterson, R., and Kelly, J.F. 1974. Animal models of the asthmatic state. Ann. Rev. Med. 25:53-68.

Richerson, H.B., Suelzer, M.T., Swanson, P.A., Butler, J.E., Kopp, W.C., and Rose, E.F. 1982. Chronic hypersensitivity pneumonitis produced in the rabbit by the adjuvant effect of inhaled muramyl dipeptide (MDP). Am. J. Pathol. 106:409-20.

Snipes, M.B., Boecker, B.B., and McClellan, R.O. 1983. Retention of monodisperse or polydisperse aluminosilicate particles inhaled by dogs, rats, and mice. Toxicol. Appl. Pharmacol. 69:345-62.

PARTICIPANTS IN THE WORKSHOP ON ENVIRONMENTALLY RELATED NONONCOGENIC LUNG DISEASE

March 13-18, 1983

Chairperson: James L. Whittenberger, M.D., University of California, Irvine

Cochairperson: Robert Frank, M.D., The Johns Hopkins University

Planning Committee Chairperson: Maria Pavlova, M.D., Ph.D., U.S. Environmental Protection Agency

Other Planning Committee Members:
David V. Bates, M.D., University of British Columbia
Arnold Brody, Ph.D., National Institute of Environmental Health Sciences
Philip A. Bromberg, M.D., University of North Carolina
Sam C. Marcus, National Center for Health Statistics
Roger O. McClellan, D.V.M., Lovelace Inhalation Toxicology Research Institute
Frank E. Speizer, M.D., Harvard University
Hugh B. Stamper, Ph.D., National Heart, Lung, and Blood Institute

Session I: EPIDEMIOLOGY, STATISTICS, AND RISK ASSESSMENT

Chairperson: Frank E. Speizer, M.D., Harvard University

Roy E. Albert, M.D., New York University Medical Center

Robert Bernstein, M.D., Centers for Disease Control

Andrew Churg, M.D., University of British Columbia

Benjamin G. Ferris, Jr., M.D., Harvard School of Public Health

Frank Green, M.D., National Institute for Occupational Safety and Health

Meryl Karol, Ph.D., University of Pittsburgh

Morton Lippmann, Ph.D., New York University Medical Center

Sam C. Marcus, National Center for Health Statistics

John M. Peters, M.D., University of Southern California

Jonathan M. Samet, M.D., University of New Mexico

James Ware, Ph.D., Harvard School of Public Health

Session II: CLINICAL RESEARCH

Chairperson: David V. Bates, M.D., University of British Columbia

Homer A. Boushey, Jr., M.D., University of California Medical Center, San Francisco

Philip A. Bromberg, M.D., University of North Carolina

Sonia A. Buist, M.D., Oregon Health Sciences

Benjamin C. Ferris, Jr., M.D., Harvard School of Public Health

Robert Frank, The Johns Hopkins University

Robert F. Hyatt, M.D., Mayo Clinic

Harold A. Menkes, M.D., The Johns Hopkins University Hospital

David C. Muir, M.D., McMaster University

Marvin Sackner, M.D., Mount Sinai Medical Center

Thomas J. Smith, Ph.D., Harvard School of Public Health

Lynn M. Taussig, M.D., Arizona Health Sciences Center

Session III: BASIC AND ANIMAL RESEARCH

Chairperson: Roger O. McClellan, D.V.M., Lovelace Inhalation Toxicology Research Institute

Drummond Bowden, M.D., University of Manitoba

Joseph D. Brain, SD HYG, Harvard School of Public Health

Arnold Brody, Ph.D., National Institute of Environmental Health Sciences

Allen B. Cohen, M.D., University of Texas Health Center

Albert M. Collier, M.D., University of North Carolina

Donald L. Dungworth, Ph.D., University of California, Davis

Carl Franzblau, Ph.D., Boston University School of Medicine

Joe L. Mauderly, D.V.M., Lovelace Inhalation Toxicology Research Institute

Fred Miller, Ph.D., U.S. Environmental Protection Agency

Robert Phalen, Ph.D., University of California, Irvine

Hal B. Richerson, M.D., University of Iowa Hospitals

Chapter 4

SUMMARY OF THE SYMPOSIUM ON EXPOSURE ASSESSMENT: PROBLEMS AND PROSPECTS

On September 13-14, 1982, the Task Force, in conjunction with the Scientific Liaison Staff of the Food and Drug Administration, sponsored a symposium at the National Institutes of Health, entitled "Exposure Assessment: Problems and Prospects." The various models and perspectives presented by persons from Government, academia, and clinical research institutions reflected the difficulty of assessing human exposures to toxic substances. (The agenda and participants are included at the end of this chapter.) Determination of exposure is an important component of the Task Force mandate to determine and quantify the relationship between environmental pollutants and human cancer and heart and lung disease.

The following pages include a general discussion of the contemporary role of exposure assessment and a summary of the papers presented at the symposium. The full text of most of the presentations, with the discussion that followed, will be published in early February 1984 as issues 1 and 2 of Volume 21 of the *Journal of Clinical Toxicology*.

BACKGROUND

Technological development, a beneficial and, therefore, a desirable consequence of science carries with it certain risks. Humans and their environment are exposed to the hazardous products and conditions inherent in technological development.

Until the 1960s, the legislative and regulatory tendency was to attempt to assign technologies and their products to one of two categories--safe or risky. Little attention was focused on gradations of risk.

During the last two decades, there has been increased public and official concern about public health and environmental risks inherent in the introduction of new technologies. Products and situations are now less likely to be considered either risky or safe per se, but rather more or less risky in a comparative sense. Increasingly, legislation reflects a growing appreciation and a growing public demand for more delicately poised determinations of relative risks. A consequence of this change in public and official perspective has been an augmentation of effort in risk assessment, which has led to a greater understanding that the determination of human or environmental exposure to technological products or conditions is a distinct and necessary step in the determination of relative risks.

Exposure assessments are performed for a variety of reasons and in a variety of settings. They may be performed as abstract scientific enterprises to study the advantages and the limitations of procedures in the conduct of scientific research and in academic environments. These determinations help develop and are themselves promoted by statistics and a variety of physical and chemical disciplines, involving the study of diffusion, reaction kinetics, instrumental analysis, and operations research.

Exposure assessments are also performed in the regulatory milieu, which is an important area of current public interest. Finally, exposure determinations are performed in the legal milieu, specifically in tort litigation.

Given these different reasons for assessing exposure and the different settings where assessments are undertaken, it is not surprising that research to improve methods of exposure determination is not more focused on specific issues. This lack of focus is a function of the different use classes of potentially toxic chemicals, the variety of means through which people come in contact with them, and the ways by which current laws assign public health protection responsibilities to the different regulatory Agencies of the Government. To differing degrees, Government Agencies are concerned about the potential for human exposure to a variety of substances that can be loosely classified as follows:

- Commercial or industrial agents
- Food use chemicals, such as direct food additive materials used for food processing and materials used in food packaging
- Medicinals
- Agricultural and commercial poisons, such as pesticides, fungicides, and rodenticides
- Environmental contaminants, manmade or natural, such as fungal toxins, power plant stack emissions, and automotive exhaust pollutants.

People may come in contact with these agents in air, water, food, and soil.

Responsibility for managing the potential health and environmental risks of exposure to such agents falls within the purview of several Agencies. Although Agencies do have specific responsibilities, exposures to toxic substances may occur through several media and routes, thus creating a network of overlapping responsibilities and complicating the problem of determining and controlling exposures.

In the many models of risk estimation, risk is assumed to be a product of a term presumably measuring the potential of a substance to cause human disease or environmental damage and a term presumably measuring human or environmental exposure to that substance. The term measuring exposure may be called dose, dose level, dose rate, ambient level, or a variety of other nonspecific names.

The definition of exposure is usually obscured by a series of assumptions that make it difficult to compare animal exposures used to determine risks (bioassays) and actual human exposures that are the reasons for risk assessments. These assumptions are necessary because of the scarcity of data on human and environmental exposures. It was this fundamental problem--the lack of data about human exposure to toxic substances--that was the focus of the Symposium on Exposure Assessment.

SYMPOSIUM OVERVIEW

The symposium planning committee assembled speakers from the regulatory and health Agencies and from academia to present an overall view of exposure determination procedures used in various settings to meet various exposure control responsibilities. It was requested that the presentations address the following major areas of concern:

- Sources of available data on exposure
- Models and experimental methods for exposure determination
- Any special case studies of exposure assessment.

Each presentation was followed by a discussion period to encourage interdisciplinary interactions.

Several participants noted that although EPA has a large volume of data on the physical environment, such data are of limited usefulness in estimating the exposure of people to pollutants. There are two complementary approaches used by EPA to estimate exposure to environmental pollutants: modeling of component exposures and human activities and measuring of actual exposures in the environment. Exposure assessment is an important factor in identifying susceptible populations and in designing better regulatory strategies. However, seldom do investigators have the means.

Several presentations dealt with the fact that exposure determinations are necessary to construct and use dose-response curves. However, investigators are not often able to accurately determine human exposures to toxic agents. Various methods and means of estimating exposure, within the constraints of available data bases and resources were described, including the following:

- Job-exposure matrices, which are cross-classifications of industry-specific job titles with agents to which persons in the jobs are exposed
- Agency and interagency data bases, such as the NIOSH National Occupational Hazard Survey and the National Occupational Exposure Survey and the NCHS National Health and Nutrition Examination Survey
- Industry efforts to collect and record exposure information.

Other presentations outlined the major problems involved in attempting to estimate exposures to food additives or contaminants. Representatives from the FDA Bureau of Foods described the data sources that provide information on populations, food intake, and food analyses; the monitoring program for chemical contaminants in food; and nationally representative surveys to provide estimates of consumption of food substances for U.S. population groups. A presentation by an NCI investigator described methods of assessing diet in light of evidence that dietary patterns and nutritional status are related to cancer risk.

Although it might be expected that determination of human exposure to drugs would be relatively straightforward because drugs are usually administered under controlled conditions, representatives from the FDA National Center for Drugs and Biologics enumerated the following problems in assessing human drug exposures:

- Exposure is usually irregular, intermittent, and variable.
- Most persons experience multiple or combined drug exposures.
- Many drugs have various metabolites with a different range of effects.
- There is confusion associated with drug names and measurement systems.

Approaches to solving these problems include marketing research, case control and drug exposure histories, and record linking using computerized data bases, such as those developed by health maintenance organizations and Medicaid.

Also discussed were methods of relating drug surveillance to environmental exposure in terms of the consequences to humans. Case control studies were presented as a method for relating drug exposures to the risk of cancer and birth defects. Factors that adversely influence the outcome of pregnancy and that should be considered in a total exposure assessment were described.

Another group of presentations dealt with the complexity of attempting to predict the fate of environmental contaminants or commercially and industrially used chemicals, once they have been released into the environment. Representatives from EPA discussed the following subjects:

- Techniques used to assess human exposures to environmental toxins and specific issues related to estimation of multimedia exposure, characterization of uncertainty, and estimation of whole-body dose
- The EPA program to evaluate environmental exposure to priority pollutants and procedures for integrating information on chemical production and use patterns, environmental fate and transport properties, exposure levels, ambient concentrations, and predominant pathway of exposure
- Multimedia mathematical models to predict the exposure concentrations of many chemicals simultaneously
- A predictive method for assessing total exposure from air, water, and food to various toxicants associated with the synfuel industry
- A computer program using activity patterns to calculate carbon monoxide exposures of the population. (This is an alternative approach to doing field surveys of populations using personal monitors.)

Finally, the symposium provided an overview of several NCHS data bases that may include information useful to assessing human exposure to environmental pollutants:

- National mortality data system
- Population-based household surveys
- National Health and Nutrition Examination Survey.

Although the information in these data systems was not collected specifically to provide estimates of exposure, these data systems can offer clues to exposure-disease relationships.

While the symposium elucidated the many problems involved in assessing human exposure to toxic substances in the environment, many innovative approaches to dealing with the problems were described and shared. It was agreed that by pooling resources and cooperatively addressing common problems, much progress can be made in refining the science of exposure assessment.

EXPOSURE ASSESSMENT: PROBLEMS AND PROSPECTS

Planning Committee: Constantine Zervos, FDA, Chairperson
Patricia Golden, NCHS
Thomas Mason, NCI

AGENDA

NIH Building 31C, Conference Room 6

Monday, September 13, 1982

Constantine Zervos, FDA	Introductory Remarks
Courtney Riordan, U.S. EPA	Keynote Speech: Human Exposure to Environmental Pollutants
Shelia Hoar, NCI	Job Exposure Matrix Methodology
James Falco, U.S. EPA	Exposure Assessment Techniques Used by EPA
Michael Slimak, U.S. EPA	Environmental Pathways of Exposure to 129 Priority Pollutants
Kenneth Hedden, U.S. EPA	Comparative Multimedia Transport Models
Alan Moghissi, U.S. EPA	Multimedia Exposure: Application to Synfuel Industry
Wayne Ott, U.S. EPA	Exposure Estimates Based on Computer Generated Activity Patterns
Sandra Stinnett, University of North Carolina at Chapel Hill	Optimal Use of Existing Data for Exposure Assessment in Etiologic Studies of Cancer
Regina Ziegler, NCI	Assessing Diet in Case-Control Studies of Cancer
David J. Wagstaff, FDA	Food Contaminants Exposure Assessment in the United States

AGENDA (Concluded)

Tuesday, September 14, 1982

Garfield Biddle, FDA	Exposure Assessment as a Tool in Regulatory Assessment to Ensure Food Safety
Elizabeth Yetley, FDA	Data Sources and Methods for Estimating Consumption of Food Substances
Todd Frazier, NIOSH	NIOSH Occupational Health and Hazard Surveillance Systems
Michael Gough, OTA	Sources and Interpretation of Asbestos Exposure Data
Judith Jones/ Diana Kennedy, FDA	Data Sources and Methods for Ascertaining Human Exposure to Drugs
Samuel Shapiro, Boston University School of Medicine	Role of Case-Control Studies in Relation to Risk of Cancer and Birth Defects
Stephen Van de Carr, FDA	Medicaid-Drug Event Linkage Data
Howard Hoffman, NICHHD	Epidemiology of Adverse Outcomes of Pregnancy
Harry Rosenberg, NCHS	Mortality Data from the National Vital Registration System
Ronald Wilson, NCHS	Household Survey Data
Robert Murphy, NCHS	Health Examination Survey Data
Thomas Mason, NCI	Closing Remarks

Chapter 5

CONTINUING TASK FORCE ACTIVITIES

The activities of the Task Force during its sixth year continued on the course delineated by last year's reassessment of direction. As a major step toward addressing its mandate to recommend a comprehensive research program to determine and quantify the relationship between environmental pollution and human disease, the Task Force sponsored a workshop on Environmentally Related Nononcogenic Lung Disease and also a symposium, "Exposure Assessment: Problems and Prospects."

Other Task Force activities, related to information exchange and research coordination, serve to stimulate interagency cooperation. The personal interactions achieved through the meetings of the Working Group have expanded the flow of information among Agencies and Departments. Specific problem areas related to environmental cancer and heart and lung disease are addressed through the efforts of the Task Force project groups.

WORKING GROUP

A representative of the EPA Office of Research and Development chairs the Working Group, which is made up of representatives designated by the member organizations. The Working Group voted to expand through the addition of a representative from the Department of Energy as an observer; DOE was then accorded full member status in the summer of 1983. The Working Group meets approximately every 6 to 8 weeks to initiate new activities, discuss and review the progress of ongoing activities, and evaluate the outcome of completed efforts.

Information Exchange

The exchange of information is inherent to the interagency/interdepartmental nature of the Task Force. When the members of the Working Group meet together, they share information about research programs and findings and enhance communication among participating organizations. Although each member organization has specific responsibilities for dealing with the environmental disease problem, many issues extend across the interests of several Agencies and, indeed, of Departments. The Task Force facilitates the broadening of perspectives unique to its members.

The Task Force is a useful mechanism for obtaining information of interest to the scientific community and the public. The Fifth Annual Report contained information about each Task Force Agency's research in environmental health, as well as enumerations of recent advances in the field and relevant research priorities.

The present report includes information developed through various Working Group-sponsored workshops and symposia. This information should be useful to the Government, the scientific community at large, and Congress.

Task Force annual reports and other documents have been distributed widely in response to requests from persons in Government, academia, industry, the general public, and Congress. Most of these documents remain available through the National Technical Information Service (NTIS). The scientific interactions fostered by the Working Group have led to the development and exchange of information, and thus the Task Force has become an effective channel of communication among participating organizations and the scientific community.

Research Coordination

The Task Force-sponsored workshops and symposia provide an important means of research coordination. The symposium, "Exposure Assessment: Problems and Prospects," and the Workshop on Environmentally Related Nononcogenic Lung Disease included presentations from representatives of most of the Task Force member organizations, as well as other Government and non-Government participants. In addition to the benefit derived from the exchange of information that occurs at these conferences, the proceedings should be helpful to the Government research planning activities.

Task Force reports are distributed to various offices within the member Agencies, including research planning offices. In 1982, member Agency Directors were asked for comments on the Task Force document Summary of the Workshop on Exposure to Environmental Agents, Their Metabolism and Mechanisms of Toxicity, which they had received the previous year. Responses indicated that the study of mechanisms of toxicity is considered very important to the elucidation of environment-disease relationships and the recommendations have been considered in Agency research planning.

Task Force representatives also attend meetings and conferences on subjects related to the Task Force areas of concern. For example, in February 1983, the Working Group Chairperson gave a presentation on the Task Force at the Joint Meeting on DOE and EPA Health and Environmental Risk Analysis Programs. Attendees included persons from Government, industry, and academia.

The research coordination activities of the Task Force also continued to progress on an informal ad hoc basis. Members of the Working Group exchanged various research planning and other documents, such as EPA's Five-Year Research Outlook; NCHS Working Paper Series, No. 13, Basic Data from Wave II of the National Survey of Personal Health Practices and Consequences, United States, 1980; Volume 97, No. 3 (1982) of Public Health Reports, an issue devoted to prevention and medical education and practice; and Risk Assessment in the Federal Government: Managing the Process (National Academy of Sciences 1983). In addition, the Task Force tracks publications of other interagency groups, Agencies, and institutions relevant to research on environmental factors related to cancer and heart and lung disease.

PROJECT GROUPS

Since its inception, the Task Force Working Group addressed specific areas involved in the study of environmental disease, as defined in the First Annual Report to Congress, by establishing special subgroups or project groups. The project groups include representatives from the Task Force member Agencies and other Federal Agencies that have interests in the particular subject under consideration. During its sixth year, Task Force project groups have focused on exposure to toxic agents and metabolic mechanisms, education of health professionals, and quality assurance in analytical methodology.

Exposure and Metabolic Mechanisms

The Project Group on Exposure and Metabolic Mechanisms has identified a number of research needs in the areas of exposure and metabolic mechanisms that are important in the understanding and hopefully in the solving of problems with respect to environmentally related diseases of interest to the Task Force. These research needs were enumerated in the following publications:*

- Summary of the Workshop on Exposure to Environmental Agents, Their Metabolism and Mechanisms of Toxicity: Research Needs (1981) (NTIS Accession No. PB82-212895; paper copy $13.50; microfiche $4.00)
- Position Papers from Workshop published in the Journal of Environmental Science and Health A(17)4 (1982).

During the sixth year of the Task Force, the Project Group continued to solicit and refine input from outside sources regarding the relative importance of these various research needs as areas for Task Force consideration. In order to focus on specific problems encountered in the study of exposure and metabolic mechanisms, the Project Group formed two subcommittees, one on exposure and one on metabolism.

Subcommittee on Exposure

Under the sponsorship of the Working Group, the Subcommittee on Exposure, with the Scientific Liaison Staff of the Food and Drug Administration, held the symposium, "Exposure Assessment: Problems and Prospects," summarized in

---

* Available from Technical Resources, Inc., 10215 Fernwood Road, Suite 408, Bethesda, MD 20817; (301) 493-5300.

Chapter 4. The papers will be published as a special issue of the Journal of Clinical Toxicology in February 1984.

Subcomittee on Metabolism

The Subcommittee on Metabolism is working to identify strategies for determining the importance of mechanisms of toxicity in cancer and heart and lung diseases in terms of various metabolic events. The decision to engage in this activity was based on the comments received from most of the member Agencies that mechanisms of various metabolic events were among the most important research needs identified by the Project Group in its 1981 workshop (Exposure to Environmental Agents, Their Metabolism, and Mechanisms of Toxicity).

The Subcommittee on Metabolism held several meetings during FY83, in which members reviewed the general problems in toxicity and explored ways in which metabolic and pharmacokinetic studies might aid in the interpretation and use of toxicologic and epidemiologic data. It was soon realized that no single protocol could be recommended that would be universally valid for all toxicants. It was also realized that the possible roles of metabolic and pharmacokinetic studies in the interpretation and use of toxicologic and epidemiologic studies need to be considered.

The Subcommittee discussed the fact that frequently there is no consensus on whether a given response actually constitutes an adverse effect. Indeed the selection of the responses to be used in the diagnosis of toxicity remains an important problem in toxicology.

In addition, the Subcommittee perceived no consensus among toxicologists or investigators of xenobiotic metabolism on a standard protocol for metabolic and pharmacokinetic studies. Indeed, a protocol that works with one toxicant may be difficult to perform efficiently with another toxicant. However, the members of the Subcomittee feel that studies of the mechanisms of toxicity will be ultimately useful in improving currently used models of toxicity in animal studies. Although toxicities may be expressed through a variety of mechanisms, there are three essential characteristics of any mechanism:

1. The time course of the concentration of the active form(s) of the toxic agent at action sites

It is important to realize that the active form of the toxic agent may be the parent chemical, a metabolite of the chemical, or a toxic chemical derived from endogenous substances through a pathway induced by the agent or one in which it participates. Thus, there are three general categories of chemicals to be considered:

a. A chemical that initiates a toxicity by direct interaction with essential cellular constituents that maintain the metabolic function or genetic integrity of cells (e.g., heavy metals and direct alkylating agents such as nitrogen mustards) or govern the release or effectiveness of physiological control factors (e.g., tyramine, agonists, and antagonists).

b. A chemical that requires metabolic activation to a toxic entity that can interact with key cellular components (e.g., suicide enzyme inhibitors, the conversion of aromatic hydrocarbons to epoxides, the conversion of arylamides to N-hydroxy and imidoquinone metabolites).

c. A chemical that participates in a reaction that generates products that cause toxicity (e.g., superoxide anion radical, hydrogen peroxide, and lipid peroxides).

2. The kinetics of the interaction between the active form(s) of the toxicant and the action sites

The active form of the toxicant may combine either reversibly or irreversibly with action sites. If the reaction is reversible, alteration of the action sites may persist only as long as the active form of the toxicant is present in the body; if the reaction is irreversible, the effects on the action sites may persist long after the active form has left the body.

3. The kinetics of the sequence of events resulting from the above interaction that occurs before the toxicity is manifested

The interaction of the active form of the toxicant with action sites may lead to a series of events before the toxicity is manifested. For example, it is thought that an initiator of carcinogenesis combines with cellular DNA to form adducts, some of which may be repaired, but others of which lead to miscoding during DNA replication and, thereby, to cell transformations.

Because of the many different kinds of mechanisms by which chemicals can cause toxicities and because there can be marked individual, strain, and species differences in any or all of the three parts of the mechanisms, it is important to learn the relative importance of the three parts of a mechanism in contributing to interspecies differences and individual variations in the human population in the incidence and severity of the toxicity. The relative importance of the three parts, however, may vary with the animal species being compared, and answers to solving problems in interspecies differences will not be obtained easily.

The subcommittee believes that studies on metabolism and pharmacokinetics should be designed to

- Differentiate toxicities that are caused by the parent chemical from those that are caused by metabolites and aid in identifying the sequence of events by which a given toxicity is manifested
- Identify the form(s) of the chemical that causes a given toxicity
- Develop dosage regimens that minimize the interspecies differences in concentration of the active forms in order that the contributions of the other parts of the mechanism to interspecies differences may be assessed.

To illustrate the importance of the above objectives, the Subcommittee thought it useful to develop a series of questions for consideration. The answers to these questions should lead to the development of protocols that are effective and efficient in attaining the objectives of the toxicity studies. This information will be presented in the report, "Strategies for Determining Mechanisms of Toxicity," which is expected to be completed during the winter of 1983-84.

Therefore, the subcommittee report to the Working Group of the Task Force will focus attention on general problems of toxicity by asking appropriate questions in a logical sequence. The report will not attempt to provide answers to these questions but is intended to stimulate the development of rational approaches to solving specific problems of concern in the study of cancer and heart and lung disease.

Interagency Education Program Liaison Group

The Interagency Education Program Liaison Group (IEPLG), established as a result of a recommendation in the Task Force's Third Annual Report, has as its main goal to coordinate and stimulate Federal activities in the area of environmental and occupational health professional education. The group is an ad hoc body having the following primary objectives:

1. Improve communications among Federal health educators and scientists working in the Public Health Service, Environmental Protection Agency, and other Federal Agencies
2. Further cooperative action between Federal and non-Federal health professionals through improved communication
3. Initiate efforts to disseminate multi-Agency information to health professionals delivering patient care.

The IEPLG's initial program activity has been to acquire, organize, and annotate a comprehensive inventory of educational materials produced by Federal Agencies and Departments. The materials listed are targeted for use by physicians and other health professionals.

Although the inventory is planned to be of most use to academic health professionals, it will also be useful to other health care professionals and students. The inventory can play an important role in educating health professionals about critical Federal information resources concerned with work or environmentally related medical conditions. In addition, the inventory will aid Federal program planners in making realistic decisions relative to future educational resource needs. A workshop of Federal health educators will be convened in the spring of 1984 to review health professional education resources, their dissemination and linkage to the private sector.

The IEPLG's effectiveness is dependent on interaction and collaboration among not only Federal Agency personnel, but also the private health care community. Therefore, the IEPLG plans to organize a panel of medical educators and persons representing a cross-section of professional organizations, academic medical centers, teaching hospitals, and practicing physicians. They will consider the various issues associated with diagnosing, treating, and preventing environmentally and work related disease. The IEPLG will then organize the information, analyses, and suggestions provided by the panel and prepare, for Task Force consideration, an assessment summarizing the medical communities' findings and recommendations relevant to the gaps and needs and techniques and approaches for educating medical students, patient care practitioners, and other health professionals. The anticipated goal of this effort will be to suggest strategies and needs relative to the dissemination and use of existing health education resources.

The IEPLG's interests and activities are supportive of the national disease prevention initiative and Federal activities in prevention, which are spearheaded by the Department of Health and Human Services. By compiling a bibliography of Federal educational materials and devising dissemination networks, the IEPLG seeks to contribute to increasing the awareness of health professionals about factors in the environment that may affect health. This effort is directly relevant to the attainment of some of the specific health objectives for the Nation, described in the DHHS publication, Promoting Health/Preventing Disease (1980).

These IEPLG activities are also directly related to the third recommendation contained in the Task Force's Fifth Annual Report to Congress (1982, p. 18): "Professional medical organizations and Federal Agencies with interests in environmental health should be encouraged to coordinate their efforts towards establishing joint initiatives to promote the education of medical and other health care students and practitioners in environmental disease prevention."

Quality Assurance in Analytical Methodology

To determine the relationship between environmental pollution and human cancer and heart and lung disease, measurements must be carried out relating to exposure, metabolism, accumulation, and excretion of pollutants and metabolites. Because errors in the measurement of pollutants at the trace level in complex environmental and biological media may be potentially large, systems of quality assurance are needed to ensure the reliability and comparability of analytical results.

The Task Force Working Group established the Project Group on Quality Assurance in Analytical Methodology to focus efforts toward attaining reliable and comparable data. The Project Group is pursuing the following primary objectives:

- Promote and foster interagency cooperation in the development of analytical methodology to attain reliable and compatible data
- Reconcile by consensus any divergent views among the participating Agencies on particular regulatory analytical methods that are important to the protection of public health and the environment.

The intended use of analytical data determines the level of accuracy required in scientific measurements. The reliability of scientific data depends on proper sampling. Although the Agencies may use different analytical techniques, all Task Force members contribute to and draw conclusions from the same body of analytical data.

An initial effort of the Project Group to promote more reliable data is the establishment of an inventory of available chemical and biological standard reference materials (SRMs) that can be used in quality assurance programs. A reference material may be defined as a material or substance, one or more properties of which are sufficiently well established to be used for the calibration of an apparatus or the verification of a measurement method. SRMs are important in quality assurance systems linking data obtained in different laboratories.

The three types of reference materials in common use are as follows:

1. Biological Matrix Reference Materials

   Matrix reference materials are essentially identical to the actual samples being measured and are intended to reflect measurement problems (e.g., concentrations of constituents and types of interferences) that closely resemble those of the test specimen.

2. Simulated Reference Materials

   Simulated reference materials have properties close to the test specimens and are used to simulate analytical problems in the field.

3. Pure Materials

   Pure material reference materials are used to ensure proper identification of chemical species and to prepare simulated reference materials.

The Project Group seeks to promote quality assurance procedures that ensure that analytical data used in support of surveillance, regulatory, and environmental health programs are accompanied by statements of confidence intervals and are traceable to reference standards and valid analytical methodologies.

The ultimate objective of establishing a comparable data base will not be achieved unless the quality assurance precepts adopted by Task Force members are extended to Government contract laboratories. The second area of Project Group concern is development of quality assurance criteria to be included in instructions for contract laboratories developing scientific data for Government use. Contract laboratories operating through a competitive bidding process must have a quality assurance program written into the description of work in order to assure rigorous quality assurance expectations.

To assure this, the Project Group proposes to incorporate quality assurance criteria into the requests for proposals and instructions for contract laboratories generating scientific data for Government use. The intent is to draft model scientific contracts with guidelines that enhance the quality of scientific results. The Project Group is considering a quality assurance workshop during FY84 to achieve these objectives.

Finally, the Project Group has focused on the need to highlight quality assurance principles in the basic training curricula used by educators of public health scientists. Assisting teachers in their formal efforts to expose trained scientists to quality assurance concepts would enhance the perception of the special need for data quality in the health science areas.

To approach this goal, the group has set three phases:

1. Information gathering
2. Selection of elements to be recommended for discussion of inclusion in curricula
3. Communication with professional health science educators and provision of educational material to them.

The first phase is underway: a library search for quality assurance educational materials has been performed and abstracts of identified documents are being examined. Advice will be sought from quality assurance project groups of various professional societies. Once the information is collected, the group will select the most appropriate materials. Final phases of this effort are expected to be carried out through coordination with the Interagency Education Program Liaison Group.

Appendix A

PERTINENT SECTION OF PUBLIC LAW 95-95

Appendix A

SECTION 402 OF PUBLIC LAW 95-95

Clean Air Act Amendments of 1977

"INTERAGENCY COOPERATION ON PREVENTION OF ENVIRONMENTAL CANCER AND HEART AND LUNG DISEASE

Sec. 402(a) Not later than three months after the date of enactment of this section, there shall be established a Task Force on Environmental Cancer and Heart and Lung Disease (hereinafter referred to as the 'Task Force'). The Task Force shall include representatives of the Environmental Protection Agency, the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute [for] Occupational Safety and Health, and the National Institute [of] Environmental Health Sciences, and shall be chaired by the Administrator (or his delegate).

(b) The Task Force shall--

(1) recommend a comprehensive research program to determine and quantify the relationship between environmental pollution and human cancer and heart and lung disease;

(2) recommend comprehensive strategies to reduce or eliminate the risks of cancer or such other diseases associated with environmental pollution;

(3) recommend research and such other measures as may be appropriate to prevent or reduce the incidence of environmentally related cancer and heart and lung diseases;

(4) coordinate research by, and stimulate cooperation between, the Environmental Protection Agency, the Department of Health, Education, and Welfare, and such other Agencies as may be appropriate to prevent environmentally related cancer and heart and lung diseases; and

(5) report to Congress, not later than one year after the date of enactment of this section and annually thereafter, on the problems and progress in carrying out this section."

Appendix B

MEMBERS OF THE TASK FORCE, WORKING GROUP, AND ITS PROJECT GROUPS

TASK FORCE PLENARY

EPA	William Ruckelshaus, Administrator	Chairperson
	Maria Pavlova, Office of Research and Development	Working Group Chairperson
	A. Alan Moghissi, Office of Research and Development	
NCI	Vincent T. DeVita, Director	
	Herman F. Kraybill, Scientific Coordinator for Environmental Cancer, Division of Cancer Cause and Prevention	
NHLBI	Claude J.M. Lenfant, Director	
	Suzanne S. Hurd, Acting Director, Division of Lung Diseases	
CDC	William H. Foege, Director	
	Clark W. Heath, Jr., Director, Program Development Office, Office of the Director	
CDC: NIOSH	J. Donald Millar, Director	
	Kenneth Bridbord, Director, Office of Extramural Coordination and Special Projects	
NIEHS	David P. Rall, Director	
	Raymond E. Shapiro, Assistant Director for Toxicology Coordination	
NCHS	Manning Feinleib, Director	
	Sam C. Marcus, Special Assistant to the Director	
FDA	Arthur Hull Hayes, Jr., Commissioner	
	Allen H. Heim, Director, Office of Science Coordination, Office of the Commissioner	
DOE	Charles W. Edington, Associate Director Office of Health and Environmental Research, Office of Energy Research	
	J.W. Thiessen, Deputy Associate Director Office of Health and Environmental Research, Office of Energy Research	

Preceding page blank

WORKING GROUP

EPA	Maria Pavlova, Office of Research and Development	Chairperson
	A. Alan Moghissi, Office of Research and Development	
NCI	Herman F. Kraybill, Scientific Coordinator for Environmental Cancer, Division of Cancer Cause and Prevention	
	Morris I. Kelsey, Assistant to the Scientific Coordinator for Environmental Cancer, Division of Cancer Cause and Prevention	
NHLBI	Suzanne S. Hurd, Acting Director, Division of Lung Diseases	
	Zakir H. Bengali, Division of Lung Diseases	
	Paul Leaverton, Acting Associate Director, Epidemiology and Biometry, Division of Heart and Vascular Diseases	
	A. Richey Sharrett, Medical Officer, Division of Heart and Vascular Diseases, Epidemiology Branch	
CDC	Clark W. Heath, Jr., Director, Program Development Office, Office of the Director	
	George Hardy, Assistant Director, Washington Office	
CDC: NIOSH	Kenneth Bridbord, Director, Office of Extramural Coordination and Special Projects	
NIEHS	Wilford L. Nusser, Associate Director for Extramural Programs	
	Raymond E. Shapiro, Assistant Director for Toxicology Coordination	
NCHS	Sam C. Marcus, Special Assistant to the Director	
FDA	Lois Ann Beaver, Staff Scientist, Office of Science Coordination, Office of the Commissioner	
	Allen H. Heim, Director, Office of Science Coordination, Office of the Commissioner	

HRSA	Max Lum, Medical Education Specialist, Division of Medicine, Bureau of Health Professions	
DOE	Nathaniel Barr, Manager, Health and Environmental Risk Analysis Program, Office of Health and Environmental Research	

PROJECT GROUPS

Exposure and Metabolic Mechanisms

NCI	Morris I. Kelsey, Assistant to the Scientific Coordinator, Division of Cancer Cause and Prevention	Chairperson
	Herman F. Kraybill, Scientific Coordinator for Environmental Cancer, Division of Cancer Cause and Prevention	
	Elizabeth K. Weisburger, Assistant Director for Chemical Carcinogenesis, Division of Cancer Cause and Prevention	
	Thomas J. Mason, Chief, Population Study Section, Environmental Epidemiology Branch, Division of Cancer Cause and Prevention	
EPA	Lance Wallace, Environmental Scientist, Office of Monitoring Technology Support, Office of Research and Development	
NHLBI	James Gillette, Chief, Laboratory of Chemical Pharmacology	
CDC	Jean French, Health Scientist, Chronic Disease Division, Center for Environmental Health	
	Clark W. Heath, Jr., Director, Program Development Office, Office of the Director	
CDC: NIOSH	Richard W. Niemeier, Section Chief, Acute and Subchronic Toxicology, Divison of Biomedical and Behavioral Sciences (Cincinnati)	
	Harry B. Plotnick, Section Chief, Mechanics of Industrial Disease, Division of Biomedical and Behavioral Sciences	
	Pervis C. Major, Chief, Immunology Section, Division of Respiratory Disease Studies (Morgantown)	
NIEHS	Larry G. Hart, Assistant to the Director	

PROJECT GROUPS (Continued)

NCHS	Sam C. Marcus, Special Assistant to the Director	
USDA	John E. Spaulding, Director, Residue Evaluation and Surveillance Division, Food Safety and Quality Service	

Subcommittee on Exposure

NCI	Thomas J. Mason, Chief, Population Study Section, Environmental Epidemiology Branch, Division of Cancer Cause and Prevention Aaron Blair, Acting Head, Occupational Studies Section, Environmental Epidemiology Branch, Division of Cancer Cause and Prevention Morris I. Kelsey, Assistant to the Scientific Coordinator, Division of Cancer Cause and Prevention	Chairperson
EPA	Lance Wallace, Environmental Scientist, Office of Monitoring Technology Support, Office of Research and Development	

Subcommittee on Metabolism

NHLBI	James Gillette, Chief, Laboratory of Chemical Pharmacology	Chairperson
EPA	Amy Rispin, Hazard Evaluation Division, Office of Pesticide Programs, Office of Pesticides and Toxic Substances	
NCI	Morris I. Kelsey, Assistant to the Scientific Coordinator, Division of Cancer Cause and Prevention Herman F. Kraybill, Scientific Coordinator for Environmental Cancer, Division of Cancer Cause and Prevention Elizabeth K. Weisburger, Assistant Director for Chemical Carcinogenesis, Division of Cancer Cause and Prevention	
NIEHS	Larry G. Hart, Assistant to the Director	

PROJECT GROUPS (Continued)

Project Group on Quality Assurance in Analytical Methodology

FDA	W. Michael Rogers, Director, Drugs, Devices, and Radiological Health Branch	Chairperson
	Lois Ann Beaver, Staff Scientist, Office of Science Coordination, Office of the Commissioner	
	William Horwitz, Acting Director, Science Policy Staff, Bureau of Foods	
EPA	Darwin Wright, Quality Assurance Management Staff	
CDC	David D. Bayse, Director, Clinical Chemistry Division	
NIEHS	Phillip Albro, Environmental Chemistry Branch	
NBS	Curt Reimann, Acting Deputy Director for Resources and Operations	

Interagency Education Program Liaison Group

HRSA	Max Lum, Medical Education Specialist, Division of Medicine, Bureau of Health Professions
NIEHS	Wilford L. Nusser, Associate Director for Extramural Programs
FDA	Lois Ann Beaver, Staff Scientist, Office of Science Coordination, Office of the Commissioner

Appendix C

LIST OF PUBLICATIONS* ORIGINATING FROM THE TASK FORCE ON ENVIRONMENTAL CANCER AND HEART AND LUNG DISEASE

Environmental Cancer and Heart and Lung Disease, Fifth Annual Report to Congress, August 1982 (NTIS Accession No. PB83 155762; paper copy $16.00; microfiche $4.50).

This report describes the work of the Task Force in its fifth year and outlines plans for the future. Brief state-of-the-art summaries on the relationship between environmental factors and cancer and heart and lung disease are included. Overviews of Agency research in the area of environmental disease are presented. Recommendations are related to continuing support of the National Death Index, removal of legal impediments to epidemiologic research, and education of health professionals about environmental disease.

Environmental Cancer and Heart and Lung Disease, Fourth Annual Report to Congress, August 7, 1981 (NTIS Accession No. PB 82 200429; paper copy $12.00; microfiche $4.00).

This report discusses fourth year activities of the Task Force in the context of the environmental disease problem. It contains recommendations to Congress and research needs identified by a Task Force-sponsored workshop. A summary of an inventory of Agency-funded environmental health research at the project level is included.

Environmental Cancer and Heart and Lung Disease, Third Annual Report to Congress, August 7, 1980 (NTIS Accession No. PB 81 174716; paper copy $11.00; microfiche $3.50).

This document presents the major activities of the Task Force during its third year and describes the initial process for developing specialized recommendations relevant to the Task Force mission. In addition to the expansion of information exchange activities (and the inclusion of FDA as the eighth member), the Task Force continued to increase its efforts in the areas of environmental health education and risk assessment as enumerated in a separate report comparing the various criteria used by Federal Agencies to regulate carcinogens. An inventory of Agency-funded research at the program level is included.

---

* Most of these publications can be obtained through requests to Technical Resources, Inc., 10215 Fernwood Road, Suite 408, Bethesda, Maryland 20817; (301) 493-5300. Some Task Force reports are also available through the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, Virginia 22161.

Preceding page blank

Environmental Cancer and Heart and Lung Disease, Second Annual Report to Congress, August 7, 1979.

Progress on second year Task Force work was described. Project Groups were formed on Standardization of Measurements and Tests, Education of the Public and of Health Professionals, and Exposure and Metabolic Mechanisms. Information exchange among member Agencies of the Task Force was considered the primary basis for establishing coordination and development of interagency programs. Funding was identified and classified in each Task Force member Agency.

First Annual Report to Congress by the Task Force on Environmental Cancer and Heart and Lung Disease, August 7, 1978.

In this first report to Congress, the Task Force summarized the problem of environmental cancer and heart and lung diseases as an interagency/interdisciplinary issue that faced the Nation as of 1978. The Task Force subsequently identified six important areas of research in which early interagency cooperation could address these issues. These research areas are: standardization of measurements and tests, exposure and metabolic mechanisms for pollutants, early indicators of disease, risk assessment, education of the public and of health professionals, and strategies to protect public health.

Summary of the Workshop on Exposure to Environmental Agents, Their Metabolism, and Mechanisms of Toxicity: Research Needs, August 1981 (NTIS Accession No. PB82 212895; paper copy $13.50; microfiche $4.00).

This summary presents the full text and rationale of 72 research recommendations developed through a consensus of scientific experts at a Workshop on Exposure, Metabolism, and Mechanisms of Toxicity held in January, 1981. The document is a compilation of research needs for environmental cancer and heart and lung disease in areas such as epidemiology, exposure quantification and monitoring, metabolism, and disease processes. Both short- and long-term needs are identified in a balanced focus on basic and applied environmental disease research.

Publication of Position Papers from the Workshop on Exposure to Environmental Agents, Their Metabolism, and Mechanisms of Toxicity, July 1982.

Papers submitted by a selected team of scientists and used as background and reference sources for Workshop discussion were published as a special issue of the Journal of Environmental Science and Health, Volume 17A, Issue 4, July 1982). A wide range of topics included: initiation/promotion concepts of carcinogenesis, toxicologic interactions and pathogenesis of lung and heart disease, and total exposure models in animals and humans.

Project Inventory

Summary Report of the Project Inventory, August 1981.

This document outlines and discusses the background of previous inventories and summarizes the methodology used in compiling and categorizing information on FY80 research projects sponsored by Task Force Agencies. Descriptors, including research category, subcategory, disease endpoint, and Agency division, are used in summary matrices that present totals in terms of number of projects and funding levels.

A Detailed Profile of Task Force Member Agency Projects in Environmental Cancer and Heart and Lung Disease, 1981.

This publication presents a detailed breakdown of Agency activities and expenditures. The number of projects and dollars expended in FY80, according to category and disease endpoint, are shown for each Agency and division.

A Listing of Projects Included in the Project Inventory, 1981.

This document lists all relevant FY80 research projects and includes information on project number, project title, categorization, funding level, and contact person. The data are organized by subject area and by Agency.

Project Inventory Analysis, Draft, January 1982.

This document is based on the data compiled in the 1981 Project Inventory. It includes graphical representations of Task Force Agencies' FY80 expenditures and numbers of projects in environmental disease research. In addition, research projects are summarized and previously published research recommendations are presented.

Report of the Inventory of Federal Research Programs of Relevance to the Task Force, April 1980.

This initial inventory is a compilation of research program information from Task Force member Agencies in a common format for 115 research programs. Details pertaining to each research program are given to facilitate general coordination. Summary information on program description, resources applied, person-year effort, objectives and mandated responsibilities, activities, and future research and resource needs is included.

Directory of Federal Interagency Groups Concerned with Environmental Health

First edition, October 1979.

The document was compiled to enhance the availability of knowledge on environmental health. Information on 24 committees is included.

Second edition, April 1980.

This edition included information on 33 interagency committees and their subcommittees or components that deal with environmental health.

Third edition, December 1981 (NTIS Accession No. PB82 198227; paper copy $10.50; microfiche $4.00).

This edition contains revised listings of the interagency committees included in the 1980 Directory. Each listing includes names of committee representatives, the authorizing charter, relevant publications and accomplishments, and meeting schedule.

Directory of Exposure-Related Data Bases, 1981.

This directory provides key information on a variety of specialized exposure data bases. A description of the purpose, scope, quality of data, format, and accessibility of each data base is included.

Feasibility Plan for a Resource Center on Environmental and Occupational Health Professional Education Material, Draft, September 1981.

This report studies the issue of establishing a national center for the dissemination of available information on environmental health to both health professionals and the general public. Information is compiled on current and planned educational activities in the public sector, as well as types of materials available in the medical sector.

Feasiblity Study on Data Quality, January 1982.

The Project Group on Standardization of Measurements and Tests developed a study on quality of data produced by chemical laboratories. Chemical measurement programs were reviewed to obtain data quality indices.

A Summary of the Legislative Framework for Risk Assessment by Task Force Agencies in the Environmental Health Context, Draft, 1981.

This document compares the legislative mandates under which Federal regulatory Agencies operate when dealing with carcinogens. The report presents the criteria used in judging risk, defines a health risk, and analyzes the role of costs and benefits related to risk reduction vis-a-vis regulation.

Calendar, Monthly Issue, June 1979-December 1981.

The Calendar was distributed monthly to facilitate information dissemination within a 3-month time frame. The Calendar announced meetings, conferences, symposia, courses, public hearings, and workshops that pertained to environmental pollution and disease.

A Tracking Mechanism for Federal Research: Health Effects of Groundwater Sources of Drinking Water, 1981.

This report delineates the stages that research recommendations undergo from inception through implementation, using groundwater quality as the topic of concern. By tracing the recommendations made in the groundwater area over the past few years, the report follows subsequent plans, research projects, and findings in an attempt to analyze how Government responds to research recommendations.

Summary of the Workshop on Environmental Education Needs of Health Professionals, December 1979.

This 2-day workshop, held by the Project Group on Education of the Public and of Health Professionals, identified the needs of health professionals in environmental education. To meet these needs, the workshop participants developed action plans that were aimed at increasing health professional capabilities in effectively preventing environment-related disease. Workshop participants included representatives from health professional organizations, labor unions, and concerned Federal Agencies. The purpose of this document is to report on the activities of the Project Group before, during, and since the October 1979 workshop; to publish the methodology and summary of the workshop; and to outline the type of recommendations expected to result from the workshop output.

Recommendations on Environmental and Occupational Education of Health Professionals, April 1980.

The recommendations that resulted from a 2-day workshop on the environmental education needs of health professionals are presented in this document. These recommendations outline a strategy through which health professionals can more effectively prevent environment-related diseases. Included in the stategy are the establishment of an Interagency Education Program Liaison Group and specific recommendations addressing curriculum, faculty, students, continuing education, and research components.

A Comparison of Scientific and Procedural Bases Used by Federal Agencies for the Regulation of Carcinogens, February 1980.

This document summarizes the risk assessment activities conducted by Federal Agencies, interagency groups, scientific panels, and private groups in the field. A comparison of the scientific and procedural bases used by Federal Agencies for regulating carcinogenic substances is presented.

Report of the Project Group on Exposure and Metabolic Mechanisms, April 1980.

This report synthesizes discussions, ideas, literature searches, and proposed approaches for continuing activities of the Project Group. The Group's overall efforts are directed at establishing a mechanism to achieve interagency cooperation and developing recommendations for needed research in relating exposure to environmental pollutants, their human intake, toxicity, and metabolic fate. The Project Group enumerated nine areas where empirical research should continue.

Appendix D

ENVIRONMENTALLY RELATED NONONCOGENIC LUNG DISEASE WORKSHOP BIBLIOGRAPHY*

Abrams, W.R., Cohen, A.B., Damiano, V.V., Eliraz, A., Kimbel, P., Meranze, D.R., and Weinbaum, G. 1981. A model of decreased functional alpha-1-proteinase inhibitor. J. Clin. Invest. 68:1132-39.

Adamson, I.Y.R., and Bowden, D.H. 1981. Dose response of the pulmonary macrophagic system to various particulates and its relationship to transepithelial passage of free particles. Exp. Lung Res. 2:165-75.

Albert, R.E. 1983. Comparative carcinogenic potencies of particulates from diesel engine exhaust, coke oven emissions, roofing tar aerosols and cigarette smoke. Environ. Health Prosp. 47:339-41.

Albert, R.E., Lippmann, M., and Briscoe, W. 1969. The characteristics of bronchial clearance in humans and the effects of cigarette smoking. Arch. Environ. Health 18:738-55.

Aubry, F., Gibbs, G.W., and Becklake, M.R. 1979. Air pollution and health in three urban communities. Arch. Environ. Health 34:360-68.

Barry, B.E., Miller, F.J., and Crapo, J.D. 1982. Alveolar epithelial injury caused by inhalation of low levels of ozone. Am. Rev. Respir. Dis. 125(Suppl.):148.

Barter, C.E., and Campbell, A.H. 1976. Relationship of constitutional factors and cigarette smoking to decrease in 1-second forced expiratory volume. Am. Rev. Respir. Dis. 113:305-14.

Beck, G.J., Schachter, E.N., Maunder, L.R., and Schilling, R.S.F. 1982. A prospective study of chronic lung disease in cotton textile workers. Ann. Intern. Med. 97:645-51.

Black, L.F. 1982. Early diagnosis of chronic obstructive pulmonary disease. Mayo Clinic Proc. 57:765-72.

Blair, W.H., Henry, M.C., and Ehrlich, R. 1969. Chronic toxicity of nitrogen dioxide. II. Effects on histopathology of lung tissue. Arch. Environ. Health 18:186-92.

---

* References listed here were cited in the preparation of background materials and research needs by participants at the Workshop on Environmentally Related Nononcogenic Lung Disease, March 13-18, 1983. This listing does not represent an exhaustive literature search and should not be considered definitive or comprehensive.

Bohning, D.E., Atkins, H.L., and Cohen, S.H. 1982. Long-term particle clearance in man: normal and impaired. Ann. Occup. Hyg. 26:259-71.

Boorman, G.A., Schwartz, L.W., and Dungworth, D.L. 1980. Pulmonary effects of prolonged ozone insult in rats. Morphometric evaluation of the central acinus. Lab. Invest. 43(2):108-15.

Bouhuys, A., and van de Woestijne, K.P. 1970. Respiratory mechanics and dust exposure in byssinosis. J. Clin. Invest. 49:106-18.

Boushey, H.A., Holtzman, M.J., Sheller, J.R., and Nadel, J.A. 1980. State of the art: bronchial hyperreactivity. Am. Rev. Respir. Dis. 121:389-413.

Brain, J.D. 1970. The uptake of inhaled gases by the nose. Ann. Otol. 79:529-39.

Breeze, R.G., and Wheeldon, E.B. 1977. The cells of the pulmonary airways. Am. Rev. Respir. Dis. 116:705-77.

Brody, A.R., and Hill, L.H. 1982. Interstitial accumulation of inhaled chrysotile asbestos fibers and consequent formation of microcalcifications. Am. J. Pathol. 109:107-14.

Brody, A.R., Hill, L.H., Adkins, B., Jr., and O'Connor, R.W. 1981. Chrysotile asbestos inhalation in rats: deposition pattern and reaction of alveolar epithelium and pulmonary macrophages. Am. Rev. Respir. Dis. 123:670-79.

Brody, A.R., and Roe, M.W. 1983. Deposition pattern of inorganic particles at the alveolar level in the lungs of rats and mice. Am. Rev. Respir. Dis. 128(4):724-29.

Burge, P.S., Perks, W.H., O'Brien, I.M., Burge, A., Hawkins, R., Brown, D., and Green, M. 1979. Occupational asthma in an electronics factory: a case control study to evaluate aetiological factors. Thorax 34(3): 300-307.

Burri, P.H., and Weibel, E.R. 1977. Ultrastructure and morphometry of the developing lung. In Development of the lung, ed. W.A. Hodson. New York:Marcel Dekker, Inc. pp. 215-68.

Burrows, B., and Earle, R.H. 1969. Course and prognosis of chronic obstructive lung disease. A prospective study of 200 patients. N. Engl. J. Med. 280:397-404.

Burrows, B., Knudson, R.J., and Lebowitz, M.D. 1977. The relationship of childhood respiratory illness to adult obstructive airway disease. Am. Rev. Respir. Dis. 115:751-60.

Burrows, B., and Taussig, L.M. 1980. "As the twig is bent, the tree inclines" (perhaps). Am. Rev. Respir. Dis. 122:813-16.

Carp, H., Janoff, A., Abrams, W., Weinbaum, G., Drew, R.T., Weissbach, H., and Brot, N. 1983. Human methionine sulfoxide-peptide reductase, an enzyme capable of reactivating oxidized alpha-1-proteinase inhibitor in vitro. Am. Rev. Respir. Dis. 127(3):301-5.

Castleman, W.L., Dungworth, D.L., and Tyler, W.S. 1975. Intrapulmonary airway morphology in three species of monkeys: a correlated scanning and transmission electron microscopic study. Am. J. Anat. 142:107-21.

Chan-Yeung, M., Lam, S., and Koener, S. 1982. Clinical features and natural history of occupational asthma due to western red cedar (Thuja plicata). Am. J. Med. 72:411-15.

Cheah, K.S.E., and Grant, M.E. 1982. Procollagen genes and messenger RNAs. In Collagen in health and disease, ed. J. Weiss and M. Jayson. New York:Churchill Livingstone Press. pp. 73-180.

Churg, A. 1982. Fiber counting and analysis in the diagnosis of asbestos-related disease. Human Pathol. 13(4):381-92.

Chvapil, M. 1982. Experimental modifications in collagen synthesis and degradation and their therapeutic applications. In Collagen in health and disease, ed. J. Weiss and M. Jayson. New York:Churchill Livingstone Press. pp. 206-17.

Clyde, W.A., Jr. 1980. Experimental models for study of common respiratory viruses. Environ. Health Perspect. 35:107-12.

Cockcroft, D.W., Cotton, D.J., and Mink, J.T. 1979. Nonspecific bronchial hyperreactivity after exposure to western red cedar. Am. Rev. Respir. Dis. 119:505-10.

Cohen, A.B., and James, H.L. 1982. Reduction of the elastase inhibitory capacity of alpha-1-antitrypsin by peroxides in cigarette smoke: an analysis of brands and filters. Am. Rev. Respir. Dis. 126(1):25-30.

Colley, J.R.T. 1974. Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. Lancet (Nov.2):1031-34.

Colley, J.R.T., Douglas, J.W.B., and Reid, D.D. 1973. Respiratory disease in young adults: Influence of early childhood lower respiratory tract illness, social class, air pollution, and smoking. Br. Med. J. 3:195-98.

Commission on Professional and Hospital Activities (CPHA) and IMS America, Ltd. 1977. The hospital record study. Ann Arbor, MI:CPHA.

Corn, M., Kotsko, N., and Stanton, D. 1976. Mass-transfer coefficient for sulphur dioxide and nitrogen dioxide removal in cat upper respiratory tract. Ann. Occup. Hyg. 19:1-12.

Dalbey, W.E., Nettesheim, P., Griesemer, R., Caton, J.E., and Guerin, M.R. 1980. Chronic inhalation of cigarette smoke by Fischer-344 rats. J. Natl. Cancer Inst. 64:383-90.

Dalhamn, T., and Strandberg, L. 1961. Acute effect of sulfur dioxide on rate of ciliary beat in trachea of rabbit in vivo and in vitro, with studies on absorptional capacity of nasal cavity. Int. J. Air Water Pollut. 4:154-67.

Detels, R., Sayre, J.W., Coulson, A.H., Rokaw, S.N., Massey, F.J., Jr., Tashkin, D.P., and Wu, M.M. 1981. The UCLA population studies of chronic obstructive pulmonary disease. IV. Respiratory effect of long-term exposure to photochemical oxidants, nitrogen dioxide, and sulfates on current and never smokers. Am. Rev. Respir. Dis. 124:673-80.

Dockery, D.W., and Spengler, J.D. 1981. Personal exposure to respirable particulates and sulfates. J. Air Pollut. Control Assoc. 31:153-59.

Dockery, D.W., Ware, J.H., Speizer, F.E., and Ferris, B.G., Jr. 1982. Preliminary longitudinal analysis of pulmonary function in school children in the Six-Cities Study. Am. Rev. Respir. Dis. 125(Suppl.):145.

Dodge, R. 1982. The effects of indoor air pollution on Arizona children. Arch. Environ. Health 37(3):151-55.

Dolovich, J., and Hargreave, F. 1981. The asthma syndrome: inciters, inducers, and host characteristics (editorial). Thorax 36:641-44.

Dumouchel, W.H., and Harris, J.E. 1983. Bayes methods for combining the results of cancer studies in humans and other species. J. Am. Stat. Assoc. 78:293-308.

Emery, J.L. 1970. The postnatal development of the human lung and its implications for lung pathology. Respiration 27(Suppl.):41-50.

Eustis, S.L., Schwartz, L.W., Kosch, P.C., and Dungworth, D.L. 1981. Chronic bronchiolitis in nonhuman primates after prolonged ozone exposure. Am. J. Pathol. 105(2):121-37.

Fergusson, D.M., Horwood, L.J., Shannon, F.T., and Taylor, B. 1981. Parental smoking and lower respiratory illness in the first years of life. J. Epidemiol. Community Health 35:180-84.

Ferris, B.G., Jr., Speizer, F.E., Spengler, J.D., Dockery, D.W., Bishop, Y.M.M., Wolfson, M., and Humble, C. 1979. Effects of sulfur oxide and respirable particles on human health: methodology and demography of populations in study. Am. Rev. Respir. Dis. 120:767-79.

Ferris, B.G., Jr., Speizer, F.E., and Ware, J.H. 1981. Uses of tests of pulmonary function to measure effect of air pollutants. In Measurement of risks, ed. G.G. Berg and H.D. Maillie. New York and London:Plenum Press.

Fletcher, C., Peto, R., Tinker, C., and Speizer, F.E. 1976. The natural history of chronic bronchitis and emphysema. Oxford:Oxford University Press.

Freeman, G., Juhos, L.T., Furiosi, N.J., Mussenden, R., Stephens, R.J., and Evans, M.J. 1974. Pathology of pulmonary disease from exposure to interdependent ambient gases (nitrogen dioxide and ozone). Arch. Environ. Health 29:203-10.

Freeman, G., Stephens, R.J., Crane, S.C., and Furiosi, N.J. 1968. Lesion of the lung in rats continuously exposed to two parts per million of nitrogen dioxide. Arch. Environ. Health 17:181-92.

Fry, F.A., and Black, A. 1973. Regional deposition and clearance of particles in the human nose. Aerosol Sci. 4:113-24.

Gadek, J.E., Kelman, J.A., Fells, G., Weinberger, S.E., Horwitz, A.L., Reynolds, H.Y., Fulmer, J.D., and Crystal, R.G. 1979. Collagenase in the lower respiratory tract of patients with idiopathic pulmonary fibrosis. N. Engl. J. Med. 301:737-42.

Gardner, D.E. 1980. Influence of exposure patterns of nitrogen dioxide on susceptibility to infectious respiratory disease. In Nitrogen oxides and their effects on health, ed. S.D. Lee. Ann Arbor, MI:Ann Arbor Science Publishers.

Goco, R.V., Kress, M.B., and Brantigan, O.C. 1963. Comparison of mucous glands in the tracheobronchial tree of man and animals. Ann. N.Y. Acad. Sci. 106:555-71.

Gold, W.M., Meyers, G.L., Dain, D.S., Miller, R.L., and Bourne, H.R. 1977. Changes in airway mast cells and histamine caused by antigen aerosol in allergic dogs. J. Appl. Physiol. 43:271-75.

Golden, J.A., Nadel, J.A., and Boushey, H.A. 1978. Bronchial hyperirritability in healthy subjects after exposure to ozone. Am. Rev. Respir. Dis. 118:287-94.

Goldstein, E., Peek, N.F., Parks, N.J., Hines, H.H., Steffey, E.P., and Tarkington, B. 1977. Fate and distribution of inhaled nitrogen dioxide in rhesus monkeys. Am. Rev. Respir. Dis. 115:403-12.

Harington, J.S., Allison, A.C., and Badami, D.V. 1975. Mineral fibers: chemical, physiochemical, and biological properties. Adv. Pharmacol. Chemother. 12:291-402.

Harlap, S., and Davies, A.M. 1974. Infant admissions to hospital and maternal smoking. Lancet (Mar.30):529-32.

Hazucha, M., Silverman, F., Parent, C., Field, S., and Bates, D.V. 1973. Pulmonary function in man after short-term exposure to ozone. Arch. Environ. Health 27:183-88.

Heppleston, A.G., and Styles, J.A. 1967. Activity of a macrophage factor in collagen formation by silica. Nature 214:521-22.

Higgins, M.W., Howatt, W., and Keller, J.B. 1982. Childhood determinants of adult lung function. Am. Rev. Respir. Dis. 125(Suppl.):145.

Holland, W.W., and Reid, D.D. 1965. Urban factor in chronic bronchitis. Lancet (Feb. 27):445-48.

Institute of Laboratory Animal Resources, National Research Council. 1981. Animal models for age-related diseases of man--emphysema and chronic bronchitis. In Animal models for research on aging, ed. D. Greenhouse. Washington, D.C.:National Academy Press. pp. 365-76.

Karlinsky, J.B., and Snider, G.L. 1978. Animal models of emphysema. Am. Rev. Respir. Dis. 117:1109-33.

Karol, M.H. 1981. Survey of industrial workers for antibodies to toluene diisocyanate. J. Occup. Med. 23:741-47.

Karol, M.H., Dixon, C., Brady, M., and Alarie, Y. 1980. Immunologic sensitization and pulmonary hypersensitivity by repeated inhalation of aromatic isocyanates. Toxicol. Appl. Pharmacol. 53:260-70.

Kattan, M., Keens, T.J., Lapierre, J.G., Levison, H., Bryan, A.C., and Reilly, B.J. 1977. Pulmonary function abnormalities in symptom-free children after bronchiolitis. Pediatrics 59:683-88.

Kiernan, K.E., Colley, J.R.T., Douglas, J.W.B., and Reid, D.D. 1976. Chronic cough in young adults in relation to smoking habits, childhood environment and chest illness. Respiration 33:236-44.

Kirkpatrick, M.B., Sheppard, D., Nadel, J.A., and Boushey, H.A. 1982. Effect of the oronasal breathing route on sulfur dioxide-induced bronchoconstriction in exercising asthmatic subjects. Am. Rev. Respir. Dis. 125:627-31.

Kleinman, M.T., Bailey, R.M., Chang, Y-T., Clark, K.W., Jones, M.P., Linn, W.S., and Hackney, J.D. 1981. Exposures of human volunteers to a controlled atmospheric mixture of ozone, sulfur dioxide and sulfuric acid. Am. Ind. Hyg. Assoc. J. 42:61-69.

Klika, E., and Antalikova, L. 1975. Postnatal differentiation of terminal airways of the lung in the rat and the cat. Folia Morphol. (Praha) 23:44-55.

Lee, L.Y., Bleecker, E.R., and Nadel, J.A. 1977. Effect of ozone on bronchomotor response to inhaled histamine aerosol in dogs. J. Appl. Physiol. 43:626-31.

Linn, W.S., Fischer, D.A., Medway, D.A., Anzar, U.T., Spier, C.E., Valencia, L.M., Venet, T.G., and Hackney, J.D. 1982. Short-term respiratory effects of 0.12 ppm ozone exposure in volunteers with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 125:658-63.

Linn, W.S., Medway, D.A., Anzar, U.T., Valencia, L.M., Spier, C.E., Tsao, F.S.D., Fischer, D.A., and Hackney, J.D. 1982. Persistence of adaptation to ozone in volunteers exposed repeatedly for six weeks. Am. Rev. Respir. Dis. 125:491-95.

Lippmann, M., Lioy, P.J., Leikauf, G., Green, K.B., Baxter, D., Morandi, M., Pasternack, B.S., Fife, D., and Speizer, F.E. 1983. Effects of ozone on the pulmonary function of children. In Advances in modern environmental toxicology, Vol. 5, ed. S.D. Lee, M.G. Mustafa, and M.A. Mehlman. Princeton, NJ:Princeton Scientific Publishers.

Lippmann, M., Yeates, D.B., and Albert, R.E. 1980. Deposition, retention, and clearance of inhaled particles. Br. J. Ind. Med. 37:337-62.

Lopez, M., and Salvaggio, J. 1976. Hypersensitivity pneumonitis: current concepts of etiology and pathogenesis. Ann. Rev. Med. 27:453-63.

Love, R.G., and Miller, B.G. 1982. Longitudinal study of lung function in coalminers. Thorax 37:193-97.

Luchtel, D.L. 1976. Ultrastructural observations on the mucous layer in pulmonary airways (ICCB Abstract No. 1048). J. Cell Biol. 70:350a.

Luchtel, D.L. 1978. The mucous layer of the trachea and major bronchi in the rat. SEM, Inc. Vol. II:1089-98.

Mauderly, J.L., and Hahn, F.F. 1982. The effects of age on lung function and structure of adult animals. In Advances in veterinary science and comparative medicine. Vol. 26: Respiratory system, ed. D.L. Dungworth. New York:Academic Press. pp. 35-77.

McClellan, R.O., Brooks, A.L., Cuddihy, R.G., Jones, R.K., Mauderly, J.L., and Wolff, R. 1982. Inhalation toxicology of diesel exhaust particles. Toxicological effects of emissions from diesel engines, ed. J. Lewtas. New York:Elsevier Biomedical. pp. 99-120.

McLaughlin, R.F., Tyler, W.S., and Canada, R.O. 1961. A study of the subgross pulmonary anatomy in various animals. Am. J. Anat. 108:149-65.

Mecham, R.P., and Lange, G. 1982. Antigenicity of elastin: characterization of major antigenic determinants on purified, insoluble elastin. Biochemistry 21:669-73.

Mellick, P.W., Dungworth, D.L., Schwartz, L.W., and Tyler, W.S. 1977. Short term morphologic effects of high ambient levels of ozone on lungs of rhesus monkeys. Lab. Invest. 36:82-90.

Michaeli, D., and Fudenberg, H.H. 1974. Antibodies to collagen in patients with emphysema. Clin. Immunol. Immunopathol. 3:187-92.

Miller, F.J., McNeal, C.A., Kirtz, J.M., Gardner, D.E., Coffin, D.L., and Menzel, D.B. 1979. Nasopharyngeal removal of ozone in rabbits and guinea pigs. Toxicology 14:273-81.

Monson, J.M. 1983. Assembly of procollagen mRNA translation products into pepsin-resistant structures. Collagen Rel. Res. 3:1-12.

Moorman, W.J., Chmiel, J.J., Stara, J.F., and Lewis, T.R. 1973. Comparative decomposition of ozone in the nasopharynx of beagles. Arch. Environ. Health 26:153-55.

Morey, P.R. 1979. Botanically, what is raw cotton dust? Am. Ind. Hyg. Assoc. J. 40:702-8.

Mudd, J.B., Leavitt, R., Ongun, A., and McManus, T.T. 1969. Reaction of ozone with amino acids and proteins. Atmos. Environ. 3:669-82.

Nash, A.A., and Gell, P.G.H. 1981. The delayed hypersensitivity T-cell and its interaction with other T-cells. Immunol. Today 2:162-65.

National Academy of Sciences. 1982. Byssinosis--clinical and research issues. Washington, D.C.:National Academy Press.

Olenchock, S. 1977. Animal models of hypersensitivity pneumonitis. Ann. Allergy 38:119-26.

Orehek, J., Massari, J.P., Gayrard, P., Grimaud, C., and Charpin, J. 1976. Effect of short-term, low-level nitrogen dioxide exposure on bronchial sensitivity of asthmatic patients. J. Clin. Invest. 57(2):301-7.

Page, R.C., Davies, P., and Allison, A.C. 1974. Participation of mononuclear phagocytes in chronic inflammatory diseases. J. Reticuloendothel. Soc. 15:413-38.

Parkes, W.R. 1982. Occupational lung disorders, 2nd ed. London: Butterworths.

Patterson, R., and Kelly, J.F. 1974. Animal models of the asthmatic state. Ann. Rev. Med. 25:53-68.

Pinkerton, K.E., Barry, B.E., O'Neil, J.J., Raub, J.A., Pratt, P.C., and Crapo, J.O. 1982. Morphologic changes in the lung during the lifespan of Fischer-344 rats. Am. J. Anat. 164:155-74.

Pooley, F.D. 1981. Tissue mineral identification. In Occupational lung disease, ed. H. Weill and M. Turner-Warwick. New York:Marcel Dekker. pp. 189-236.

Pullan, C.R., and Hey, E.N. 1982. Wheezing, asthma, and pulmonary dysfunction ten years after infection with respiratory syncytial virus in infancy. Br. Med. J. 284:1665-69.

Rantakallio, P. 1978. Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. Acta Pediatr. Scand. 67:621-31.

Raub, J.A., Wiester, M.J., Miller, F.J., Graham, J.A., O'Neil, J.J., and Crapo, J.D. 1982. Ozone induced alterations of pulmonary function in adult and neonatal rats. Am. Rev. Respir. Dis. 125(Suppl.):147.

Reid, L. 1977. The lung: its growth and remodeling in health and disease. Am. J. Roentgenol. 129:777-88.

Rennard, S.I., and Crystal, R.G. 1982. Special tissue collagen: lung. In Collagen in health and disease, ed. J. Weiss and M. Jayson. New York: Churchill Livingstone Press. pp. 424-44.

Richerson, H.B. 1983. Hypersensitivity pneumonitis: pathology and pathogenesis. Chem. Rev. Allergy I(4).

Richerson, H.B. 1980. Hypersensitivity pneumonitis. In Pulmonary diseases, ed. A. Fishman. New York:McGraw-Hill.

Richerson, H.B., Suelzer, M.T., Swanson, P.A., Butler, J.E., Kopp, W.C., and Rose, E.F. 1982. Chronic hypersensitivity pneumonitis produced in the rabbit by the adjuvant effect of inhaled muramyl dipeptide (MDP). Am. J. Pathol. 106:409-20.

Roberts, R.C., and Moore, V.L. 1977. State of the art: Immunopathogenesis of hypersensitivity pneumonitis. Am. Rev. Respir. Dis. 116:1075-90.

Ruoslahti, E., Engvall, E., and Hayman, E.G. 1981. Fibronectin: current concepts of its structure and functions. *Collagen Relat. Res.* 1:95-128.

Schenker, M.B., Samet, J., Batterman, S., and Speizer, F.E. 1982. An epidemiologic study of air pollution effects on childhood respiratory disease. *Am. Rev. Respir. Dis.* 125(Suppl.):145.

Schwartz, L.W., Dungworth, D.L., Mustafa, M.G., Tarkington, B.K., and Tyler, W.S. 1976. Pulmonary responses of rats to ambient levels of ozone: effects of 7-day intermittent or continuous exposure. *Lab. Invest.* 34:565-78.

Shampain, M.P., Behrens, B.L., Larsen, G.L., and Henson, P.M. 1982. An animal model of late pulmonary responses to *Alternaria* challenge. *Am. Rev. Respir. Dis.* 126:493-98.

Sheppard, D., Saisho A., Nadel J.A., and Boushey, H.A. 1981. Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects. *Am. Rev. Respir. Dis.* 123:486-91.

Sims, D.G., Downham, M.A.P.S., Gardner, P.S., Webb, J.K.G., and Weightman, D. 1978. Study of 8 year old children with a history of respiratory syncytial virus bronchiolitis in infancy. *Br. Med. J.* 1:11-14.

Snipes, M.B., Boecker, B.B., and McClellan, R.O. 1983. Retention of monodisperse or polydisperse aluminosilicate particles inhaled by dogs, rats, and mice. *Toxicol. Appl. Pharmacol.* 69:345-62.

Spector, W.G. 1974. Pulmonary fibrosis due to chemicals and particles. *Ann. N.Y. Acad. Sci.* 221:309-11.

Speizer, F.E., and Tager, I.B. 1979. Epidemiolology of chronic mucus hypersecretion and obstructive airways disease. *Epidemiol. Rev.* 1:124-42.

Stara, J.F. et al., eds. 1980. Long-term effects of air pollutants in canine species. EPA, Cincinnati, Ohio and Department of Pathology, School of Veterinary Medicine, University of California, Davis, California. EPA-600/8-80-014.

Stephens, R.J., Sloan, M.F., Evans, M.J., and Freeman, G. 1974. Early response of lung to low levels of ozone. *Am. J. Pathol.* 74:31-58.

Tager, I.B., Weiss, S.T., Rosner, B., and Speizer, F.E. 1979. Effect of parental cigarette smoking on the pulmonary function of children. *Am. J. Epidemiol.* 110:15-26.

Tager, I.B., Weiss, S.T., Speizer, F.E., and Rosner, B. 1982. Longitudinal assessment of the relationship of parents' cigarette smoking and level of pulmonary function in children. *Am. Rev. Respir. Dis.* 125(Suppl.):145.

Taeusch, H.W., and Avery, M.E. 1977. Regulation of pulmonary alveolar development in late gestation and perinatal period. Development of the lung, ed. W.A. Hodson. New York:Marcel Dekker, Inc.

Thurlbeck, W.M. 1975. Postnatal growth and development of the lung. Am. Rev. Respir. Dis. 111:803-44.

Thurlbeck, W.M. 1976. Chronic airflow obstruction in lung disease. Major problems in pathology series, Vol. 5. Philadelphia:W.B. Saunders Co.

Tukiainen, P., Taskinen, E., O. Korhola, and Valle, M. 1980. Farmer's lung. Eur. J. Respir. Dis. 61:3-11.

Tyler, N.K., Tyler, W.S., Last, J.A., Jackson, A.C., and Mouritsen, J. 1982. Structural and functional correlates of ozone in "pair fed" rats. Am. Rev. Respir. Dis. 125(Suppl.):147.

Tyler, W.S., Tyler, N.K., Jackson, A.C., Last, J.A., and Etchison, J.R. 1982. Effects of ozone on young macaques. Am. Rev. Respir. Dis. 125 (Suppl.):147.

U.S. Department of Health, Education, and Welfare, Public Health Service. 1979. Interaction between smoking and occupational exposures. In Smoking and health: A report of the Surgeon General. DHEW(PHS) Publ. No. 79-50066. pp. 7-1 to 7-25.

Vainio, H., and Hietanen, E. 1980. Role of extrahepatic metabolism. In Concepts in drug metabolism: Part A, ed. P. Jenner and B. Testa. New York:Marcel Dekker, Inc. pp. 251-84.

van As, A. 1977. Pulmonary airway clearance mechanisms: reappraisal. Editorial. Am. Rev. Respir. Dis. 115:721-26.

Vaughan, T.R., Jr., Jennelle, L.F., and Lewis, T.R. 1969. Long-term exposure to low levels of air pollution: effects on pulmonary function in the beagle. Arch. Environ. Health 19:45-50.

Wakelyn, P.J., Greenblatt, G.A., Brown, D.F., and Tripp, V.W. 1976. Chemical properties of cotton dust. Am. Ind. Hyg. Assoc. J. 37:22-31.

Wegman, D.H., Levenstein, C., and Greaves, I.A. 1982. Byssinosis: a role for public health in the face of scientific uncertainty. Am. J. Public Health 73:188-92

Wegman, D.H., Peters, J.M., Pagnotto, L., and Fine, L.J. 1977. Chronic pulmonary function loss from exposure to toluene diisocyanate. Br. J. Ind. Med. 34:196-200.

Wehner, A.P., Dagle, G.E., and Milliman, E.M. 1981. Chronic inhalation exposure of hamsters to nickel-enriched fly ash. Environ. Res. 26:195-216.

Yokoyama, E. 1968. Uptake of SO_2 and NO_2 by the isolated airways. Bull. Inst. Public Health 17:302-6.

Yokoyama, E., and Frank, R. 1972. Respiratory uptake of ozone in dogs. Arch. Environ. Health 25:132-38.

Zeiss, C.R., Wolkonsky, P., Pruzansky, J.J., and Patterson, R. 1982. Clinical and immunologic evaluation of trimellitic anhydride workers in multiple industrial sittings. J. Allergy Clin. Immunol. 70:15-18.